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July 2, 1992

Mr. Harry Daw (3HW33)
U. S. Environmental Protection Agency
Hazardous Waste Management
Removal and Enforcement Section
841 Chestnut Building
Philadelphia, PA 19107

Dear Mr. Daw:

As a follow-up to our 2 July, 1992 telephone conversation, enclosed please find a copy of the report entitled "Red Clay Creek Kinetic Uptake Study of Organic Contaminants in Stocked Trout." The enclosed copy is an updated version of the one which I previously provided to Ms. Margarete Passmore from EPA's Environmental Services Division. Please be advised that the enclosed version, although updated, is still draft, and therefore, may undergo further revision.

Also as a follow-up to our conversion, I would like to reiterate my desire to receive a copy of the "Start Action Memo" and the Administrative Order you are drafting for the NVF Kennett facility when those documents are available.

Thank you for considering Delaware's input into your program.

Sincerely,

Richard W. Greene

Richard W. Greene
Environmental Engineer

RWG:jah

cc: Margarete Passmore (w/o attachment)

Enclosure

AR100853

Delaware's good nature depends on you!

RED CLAY CREEK KINETIC UPTAKE STUDY

OF

ORGANIC CONTAMINANTS IN STOCKED TROUT

Conducted as a Component of Delaware's
Ambient Surface Water Quality Monitoring Program

Division of Water Resources
DNREC, Dover, Delaware 19903

Richard W. Greene
May, 1992

ACKNOWLEDGEMENT

Support for this work was provided by the U. S. Environmental Protection Agency and the State of Delaware General Assembly. Appreciation is extended to Mr. Roy Miller and Mr. Mark Zimmerman of the Delaware Division of Fish and Wildlife for securing the samples analyzed in this study. The Delaware Technical Services Laboratory is likewise acknowledged for their expert assistance in processing and analyzing the samples. Finally, special appreciation is expressed to those individuals who were able to review and provide comments on the manuscript.

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EXECUTIVE SUMMARY

In the spring of 1991, a small number of hatchery-raised brown trout were released to the Red Clay Clay Creek in the vicinity of Yorklyn, Delaware. Trout were recaptured at specified intervals over an approximate six-week period and analyzed for the presence of PCBs, chlorinated pesticides, and dioxins and furans in edible tissue samples.

Tissue uptake of PCBs, DDT and its metabolites, nonachlor and dieldrin were found to follow a logarithmic increase over the course of the study. Regression equations describing pollutant increase with time were developed and first order uptake rate constants were estimated.

Based upon rapid exceedance of "acceptable" tissue concentrations for several pollutants, it is concluded that the Red Clay Creek trout stocking use is nonattained. To prevent unnecessary risk to trout anglers who might consume their catch, the Red Clay Creek should not be included in Delaware's trout stocking program at the present time. A decision concerning suitability of trout stocking in the Red Clay Creek should be revisited in the future and should be considered in concert with demonstrated progress in controlling upstream pollutant sources.

Based upon the proximity of the stocking area to the PA-DE state line and the existence of documented pollutant sources in Pennsylvania, the cause of the nonattainment would appear to be toxics being transported downstream from Pennsylvania to Delaware. Continued cooperation and coordination between Pennsylvania DER, Delaware DNREC, EPA, DRBC and others will be needed to abate this problem.

INTRODUCTION

The Red Clay Creek is a small (53.3 square mile) Piedmont stream that flows out of Chester County, Pennsylvania and into northern New Castle County, Delaware in the vicinity of Yorklyn, Delaware. The stream basin is located between the Brandywine watershed to the east and the White Clay watershed to the west. The Red Clay is a tributary of the Christina River, which, in turn, empties into the Delaware River in the vicinity of Wilmington, Delaware. Figure 1 shows the regional setting of the Red Clay Creek Watershed.

The Red Clay has an unfortunate history of contamination due to toxic substances [1]. Pollutants of concern include polychlorinated biphenyls (PCBs), dioxins and furans, chlorinated pesticides, and zinc. The PCBs have been traced to an industrial source located in Kennett Square, Pennsylvania. The chlorinated pesticides (primarily DDT and metabolites) are thought to be associated with agricultural nonpoint sources in Chester County. Although the data are inconclusive, the dioxins and furans appear to be associated with the same source as the PCBs.

Because of excessive levels of the above-noted organic toxicants in fish, the Delaware Department of Natural Resources and Environmental Control (DNREC), in conjunction with the Delaware Division of Public Health (DPH), issued a public health advisory on the Red Clay in 1986. The Agency took the additional precaution of curtailing trout stocking in 1987 to further limit human exposure.

There is a desire that the Red Clay Creek will one day be of sufficient quality to stock trout again, and that conditions will warrant lifting the health advisory. Because the residence time of stocked trout in the Red Clay is expected to be fairly brief (approximately 4 to 6 weeks), there is a possibility that the trout do not have sufficient time to accumulate toxic organics to the degree that resident fish species do. The implication is that the Red Clay may be suitable for its "put-and-take" trout use but that the health advisory on resident fish is still necessary. This study was designed to help answer that question.

OBJECTIVES

The general objective of this survey was to improve the fish toxics database for the Red Clay Creek. More specific objectives included the following:

* Determine the current suitability of the put-and-take trout use of the Red Clay Creek by studying the rate of contaminant uptake in brown trout.

* Provide updated information on the level of dioxins and furans in fish in the Red Clay.

* Provide additional information concerning impacts to Delaware's fishery resources due to downstream transport of contaminants from Pennsylvania.

* Implement improved analytical methods and quality assurance procedures for fish tissue testing.

SCOPE OF MONITORING

On April 18, 1991, personnel from the Delaware Division of Fish and Wildlife (DFW) released approximately 100 brown trout into the Red Clay Creek between the state line and Yorklyn, Delaware. The release area is shown in Figure 2. Prior to releasing the trout on April 18, DFW personnel first retained six fish from those to be stocked to serve as a control sample for the study. The fish comprising the control sample were not exposed to Red Clay Creek water.

DFW returned to the Red Clay on May 7 and May 29 to recapture previously released trout. On May 7, DFW electroshocked the study area and retained six additional trout. On May 29, DFW again electroshocked the study area. This time, they secured two separate trout samples, each sample consisting of six fish. The second sample on May 29 served as a quality assurance duplicate. The absence of hold-over trout from previous years and the fact that low head dams exist directly above and below the stocking area ensured that trout recaptured as a part of this study were those released on April 18, 1992.

In total, four fish samples were secured as a part of this study in accordance with the following schedule:

DATE	# SAMPLES	#FISH/SAMPLE	RESIDENCE TIME (Days)
April 18, 1991	1	6	0
May 7, 1991	1	6	14
May 29, 1991	2	6	41

FIELD AND LABORATORY PROCEDURES

A. Field Procedures

The field protocol followed in this survey was as follows:

(i) Except for the control sample, fish were sampled with a backpack DC variable voltage electrofisher. The fish for the control were taken directly from the hold of the stocking vehicle. Six fish were retained for each sample.

(ii) The date of collection, the name of the sampler, the sample location, and the species name were recorded on the DNREC form, "Tissue Analysis Field Sheet." The weight and length of the individual specimens retained for analysis were recorded on that form.

(iii) The six fish retained for each sample were wrapped together in aluminum foil which had been rinsed first in acetone and then in distilled water. A label was placed on the outside of the foil which specified collection date, sample location, and species. The label for the control sample bore the additional identifier "CONTROL." Similarly, one of the two samples collected on May 29 bore the word "DUPLICATE."

(iv) The foil wrapped samples were placed on ice in a cooler and transported to the DNREC Technical Services Laboratory in Dover on the same day as capture. Upon arrival at the laboratory, DFW personnel transferred custody of the sample(s) and the "Tissue Analysis Field Sheet(s)" to laboratory personnel for subsequent preparation.

B. Laboratory Procedures

1. *Sample Preparation*

Each sample was dissected, homogenized, split, labeled, and frozen on the same day as receipt from the field. The specific steps followed in preparing each sample for analysis was as follows:

(i) Upon receipt of each sample, Technical Services personnel first cleaned all dissection instruments, cutting surfaces, internal surfaces of the meat grinder (homogenizer), and glassware that was to store the homogenate.

(ii) Each of the fish in the group of six was dissected by removing head, tail, scales, fins, and entrails. The skin was not removed. Parts removed were discarded and the remaining portions were combined (composited) in the meat grinder to produce a homogenate.

(iii) The homogenate produced was split into two approximately equal portions, each no less than 100 gram. Each portion was placed in a separate wide mouth glass container with a teflon lid. Both containers were labeled with the collection date, sample location, and species. One label bore the letter "A", the other, the letter "B."

(iv) The glass containers were then placed immediately in the Technical Services freezer. This process continued until all samples were retained and prepared for analysis. This resulted in the accumulation of eight containers by May 29, four labeled "A," and four labeled "B."

2. Sample Analysis

The four containers labeled "A" were shipped overnight, on dry ice, to the Triangle Laboratory in Research Triangle Park, North Carolina on May 30, 1991. The samples were accompanied by a copy of the Triangle Laboratories' "Sample

Analysis Quotation/Order Form." Triangle Laboratories analyzed the four samples for the presence of dioxins and furans using modified EPA Method 8290. The quantification limit for dioxins and furans were 1 picogram/kg wet weight (i.e., 1 part per trillion). They also analyzed each sample for percent lipid.

The four containers labeled "B" were analyzed by the DNREC Technical Services Laboratory for the presence of polychlorinated biphenyls (PCBs), chlorinated pesticides, lead, and percent lipid. PCBs and chlorinated pesticides were analyzed using modified EPA Method 608. Analytes included the following:

Aroclor 1016	o,p'-DDD
Aroclor 1221	p,p'-DDD
Aroclor 1232	o,p'-DDE
Aroclor 1242	p,p'-DDE
Aroclor 1248	o,p'-DDT
Aroclor 1260	p,p'-DDT
Aldrin	Dieldrin
alpha-BHC	Endrin
gamma-BHC	Hexachlorobenzene
cis-Chlordane	Methoxychlor
trans-Chlordane	cis-Nonachlor
	tran-Nonachlor

QUALITY ASSURANCE/QUALITY CONTROL

The overall quality assurance objectives and quality control procedures for this study are as documented in the State of Delaware Quality Assurance Project Plan: Water Quality Monitoring, March 1, 1990 [2]. Specific QA/QC measures employed in this study included the following:

* Initial and ongoing calibrations (used to establish and verify the quantification technique).

* Surrogate spike compounds (used to evaluate the analytical recovery of each sample).

* Matrix spikes (used to evaluate the effect of sample matrix on the compounds of interest).

* Field duplicate (used to evaluate field variability).

RESULTS

Table 1 presents the average lengths and weights of the trout samples. Laboratory results for PCBs, chlorinated pesticides, and lead are presented in Table 2. Laboratory results for dioxins and furans are presented in Table 3. Table 4 presents adjusted dioxin and furan concentrations for those samples and analytes for which blank contamination was reported by the contract laboratory. Adjusted values represent the difference between the concentration of the indicated analyte reported for the actual field sample and the concentration

reported for the same analyte in the laboratory blank. This adjustment was made to avoid possible false positive or bias high results.

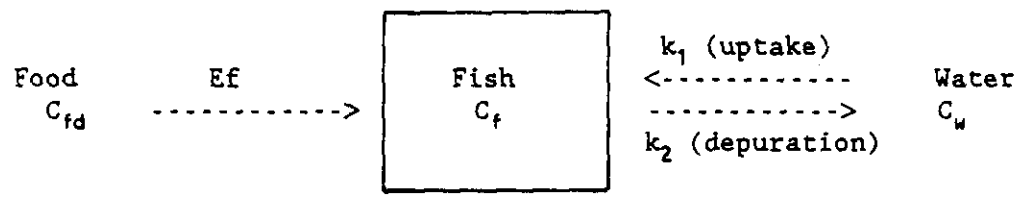
Figures 3 through 10 present plots of the natural logarithm of tissue concentration as a function of elapsed time after stocking for several pollutants considered in this study. As will be shown subsequently, semilog plots were chosen because of the excellent fit of the data to a logarithmic model of pollutant uptake. Each plot represents a best fit line to the actual field data as determined through regression analysis.

Two bold horizontal lines also appear on Figures 3 through 10. These lines represent tissue concentrations of concern for "at risk" populations (eg. expert trout fishermen and average trout fishermen). The upper line represents a fish tissue concentration associated with a 10^{-6} (one-in-a-million) incremental lifetime cancer risk for 30 years of exposure, assuming a consumption rate of 29 grams of trout per day. This scenario is taken as the reasonable worst case in this analysis. The reasonable worst case corresponds to an expert fisherman who catches and consumes an average of three fish per day during the trout season.

The lower line represents a fish tissue concentration associated with a 10^{-6} risk for 30 years of exposure, assuming a consumption rate of 4.6 grams of trout per day. This scenario is taken as the average case in this analysis. It corresponds to a fisherman who consumes an average of one trout per day during the trout season. The calculation of acceptable fish tissue contaminant concentrations for both the expert and average trout consumption scenarios is presented in Attachment A.

Determination of Uptake Rates

One of the earlier theoretical models which was postulated to describe the kinetics of pollutant uptake in fish was that of Bruggermann, et. al [3]. The model was conceptualized as shown below.



This model holds that fish can concentrate pollutants from the water column, depurate (or clear) pollutants back to the water column, or accumulate pollutants through consumption of contaminated prey. According to the model, the time rate of change of pollutant concentration in the fish can be expressed as:

$$\frac{dC_f}{dt} = EfC_{fd} + k_1C_w - k_2C_f \qquad (1)$$

where: $\frac{dC_f}{dt}$ = time rate of change of pollutant concentration in fish

C_f = concentration of pollutant in fish

C_{fd} = concentration of pollutant in food eaten by the fish

Ef = absorption efficiency for pollutant ingested by the fish

C_w = concentration of pollutant in the surrounding water

k_1 = pollutant uptake rate constant from the water to the fish

k_2 = pollutant clearance rate constant from the fish to the water

Equation (1) is a first order differential equation which, when solved (integrated), yields an expression free of derivatives which describes pollutant concentration in the fish as a function of time. It is possible, and even desirable, to simplify Equation (1) prior to attempting the integration. This can be done by assuming the first and third terms on the right-hand side of the equation are zero. Neglecting the first term is justified in situations where the density of prey available to the species of interest is low, or alternatively, when the prey are free of pollutants of concern. Biological data for the reach of interest in the Red Clay Creek suggest that food available to the stocked trout is indeed in short supply. Of course, during the normal trout season, there is an ample supply of food available to the trout in the form of bait. However, such foodstuffs are not expected to be contaminated with the pollutants under investigation in this study. Furthermore, the Red Clay was not open to trout fishing during the period of this study anyway, so the trout should not have ingested any bait, contaminated or otherwise. Neglecting the third term is believed justified because the pollutants under investigation in this study are generally considered to metabolize slowly. Certainly, the time scale over which the study was conducted is expected to be much less than the time scale of metabolic clearance. This allows us to confidently neglect depuration. In any event, it is quite clear that the rate of uptake significantly outpaces the rate of depuration for the majority of pollutants considered in this study as demonstrated by the sharp increaseg in tissue pollutant concentrations with time.

Neglecting uptake through prey and release through depuration, Equation (1) can be simplified to the following expression:

$$\frac{dC_f}{dt} = k_1 C_w \qquad (2)$$

Equation (2) can be further simplified by assuming that the concentration of pollutant in the water column, C_w, is related to the concentration in the fish, C_f, through a bioconcentration factor, K_B. The functional relationship between C_w, C_f, and K_B is written as [4]:

$$K_B = C_f/C_w \qquad (3)$$

In this case, K_B is understood to represent the capacity of a chemical to be taken up by fish from the aqueous phase, independent of the uptake kinetics. The fact that the concentration of pollutant in the water column may have varied over the course of the study is of no consequence to the value of K_B. Indeed, bioconcentration factors for most pollutants have been shown to be constant over a wide range of aqueous exposure concentrations [5]. We shall return to a discussion of bioconcentration factors later in this section.

Equation (3) can be rearranged and substituted into Equation (2) to yield the following expression:

$$\frac{dC_f}{dt} = k_1 C_f / K_B \qquad (4)$$

Equation (4) can be easily solved by first separating variables and then integrating both sides.

e.g.
$$\int_{C_{fo}}^{C_f} \frac{dC_f}{C_f} = \int_{o}^{t} \frac{k_1}{K_B}\, dt \qquad (5)$$

Carrying out the above integration yields the following relationship:

$$C_f(t) = C_{fo} \exp\,[(k_1/K_B)t] \qquad (6)$$

where: $C_f(t)$ = concentration of pollutant in fish at any time t

C_{fo} = concentration of pollutant in fish at initial time t=o

exp = base of the natural logarithm, numerically approximated as 2.718

k_1 and K_B = as define previously

t = time (past stocking)

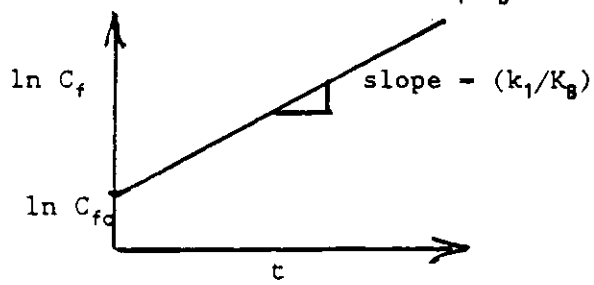
Equation (6) can be linearized by taking the natural logarithm of both sides of the equation.

e.g. $\ln C_f(t) = \ln (C_{fo} \exp\,[(k_1/K_B)t])$ (7)

Equation (7) can be expressed in its simplest form as:

$$\ln C_f(t) = \ln C_{fo} + (k_1/K_B)t \qquad (8)$$

Equation (8) can now be plotted as a straight line of the form y = ax + b where "y" is equal to $\ln C_f(t)$ and "x" is equal to t. The intercept of the line will equal $\ln C_{fo}$ and the slope will equal (k_1/K_B). This is shown below.



Equation (8) and its general plot shown above can be applied in the Red Clay Creek uptake study to determine unique functions describing pollutant uptake with time and also to determine uptake rate constants, k_1. This is done by plotting the natural logarithm of observed pollutant concentrations in the fish against elapsed time to recapture and then fitting that data to Equation (8) through least-squares linear regression [6]. The plots of the raw data and the regression equations for selected pollutants were previously introduced as Figures 3 through 10. The actual regression equations describing pollutant uptake are presented in Table 5.

Note that regression equations were not and could not be developed for all pollutants considered in this study. However, where equations could be produced, there was an excellent fit of the data to Equation (8) as indicated by correlation coefficients close to unity. This suggests that the model selected to describe the pollutant uptake process is reasonable in this case. It is important to point out, however, that even though good correlation was obtained, it would be improper to use the regression equations for times greater than the maximum recapture time (41 days). In other words, the equations are only valid over the period studied. Furthermore, they are only valid for brown trout and only valid for the Red Clay Creek in the vicinity of Yorklyn.

Now that the regression equations have been determined, it is possible to compute the uptake rate constants from the slope term, (k_1/K_B). In this case, k_1 is computed as follows:

$$k_1 = (\text{slope of regression equation})(K_B) \qquad (9)$$

To compute k_1, we first need an estimate of the bioconcentration factor, K_B. Values of K_B can be estimated through laboratory experiments or through use of equations which relate K_B, the n-octanol/water partition coefficient (log P), and the percent lipid in the fish species of interest. EPA [5] presents one such

equation based upon 122 K_B values for 13 species of fresh water and salt water species. This equation is expressed as follows:

$$\log K_B = 0.79 \log P - 0.4 - \log (7.6/x) \qquad (10)$$

In the above equation, x is the percent lipid in the fish species and tissue portion of interest. In this study, the average percent lipid in the edible portion of brown trout was 3.7%. N-octanol/water partition coefficients (log Ps) were obtained from several sources as identified in Table 6. Table 6 also lists the bioconcentration factors computed from Equation (10). Finally, Table 7 presents the uptake rate constants, k_1, computed from Equation (9).

CONCLUSIONS

Several conclusions can be drawn from Figures 3 through 10. First, virtually without exception, there was a measurable increase in the concentration of polychlorinated biphenyls and chlorinated pesticides with time. The case for furans and dioxins is far less clear. Second, based on rapid uptake of pollutants to levels in excess of the 10^{-6} risk level, it would not appear prudent at the present time to reintroduce trout stocking in the Red Clay Creek. The designated use "put-and-take trout stocking" of the Red Clay continues to be nonattained.

Based upon the proximity of the stocking area to the PA-DE stateline and the existence of documented pollutant sources in Pennsylvania, the cause of the nonattainment would appear to be toxics being transported downstream from Pennsylvania to Delaware.

FIGURE 1

REGIONAL SETTING
RED CLAY CREEK WATERSHED

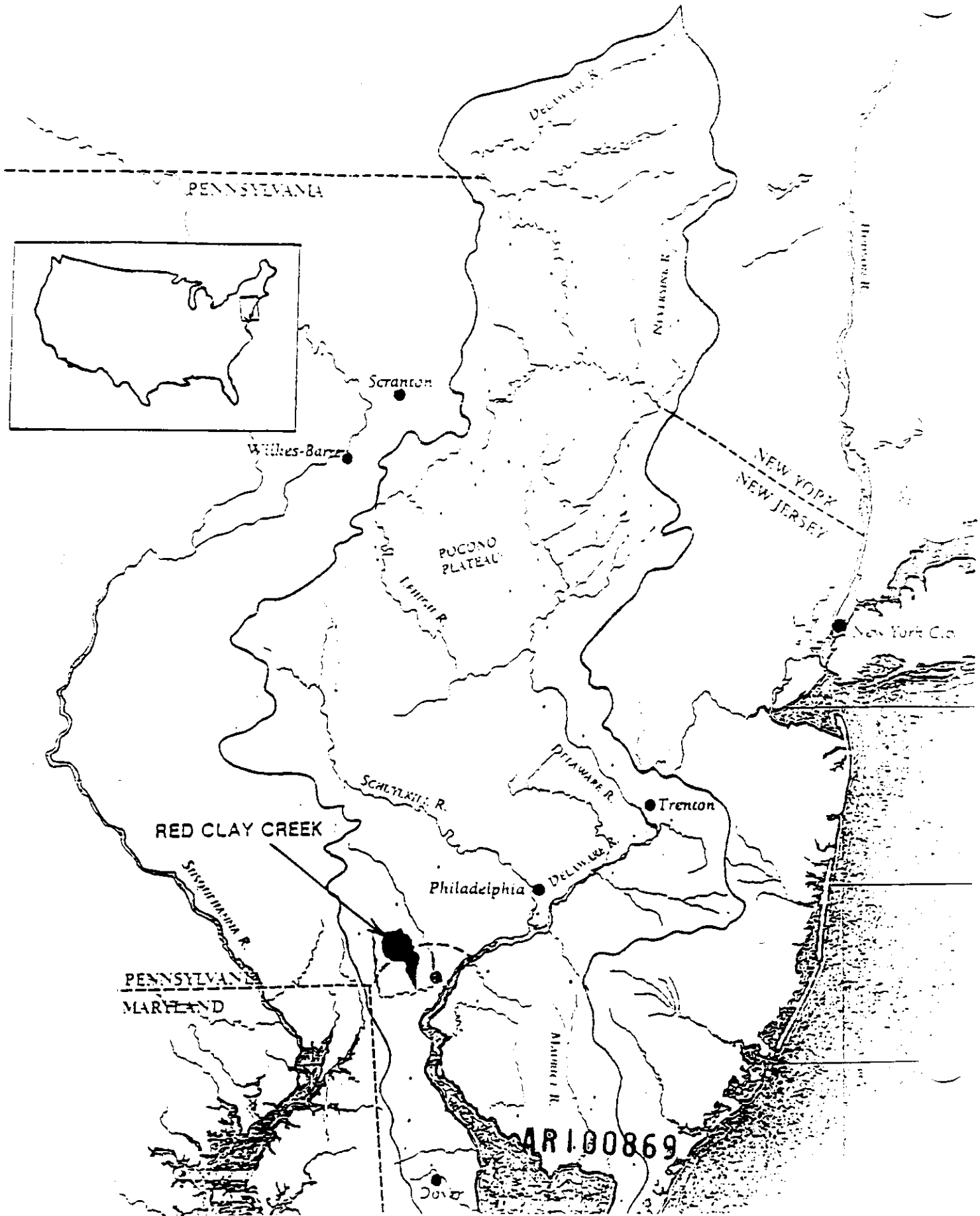


FIGURE 2

SITE LOCATION
RED CLAY CREEK KINETIC UPTAKE STUDY

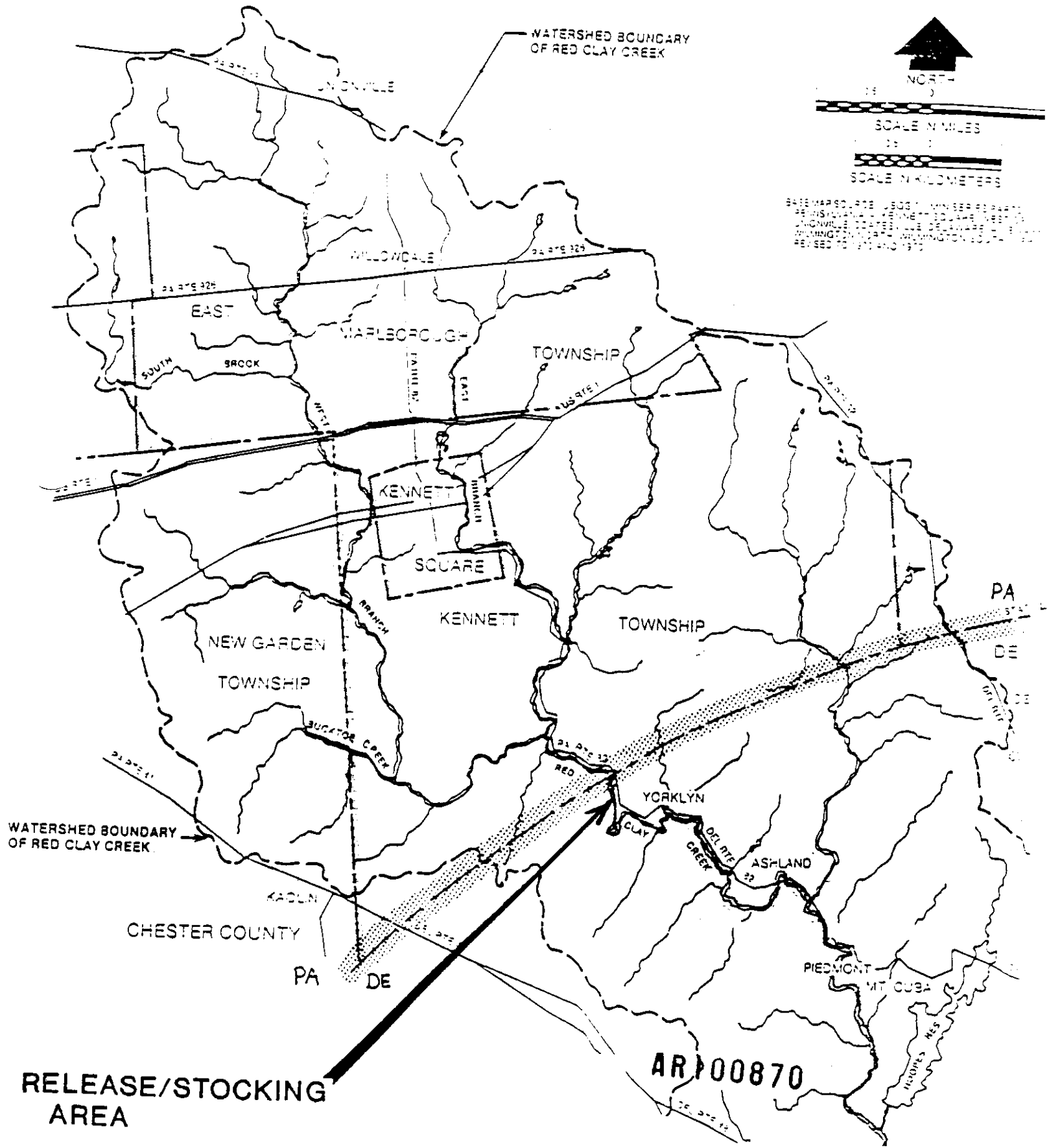


FIGURE 3

TOTAL PCB UPTAKE IN BROWN TROUT
RED CLAY CREEK

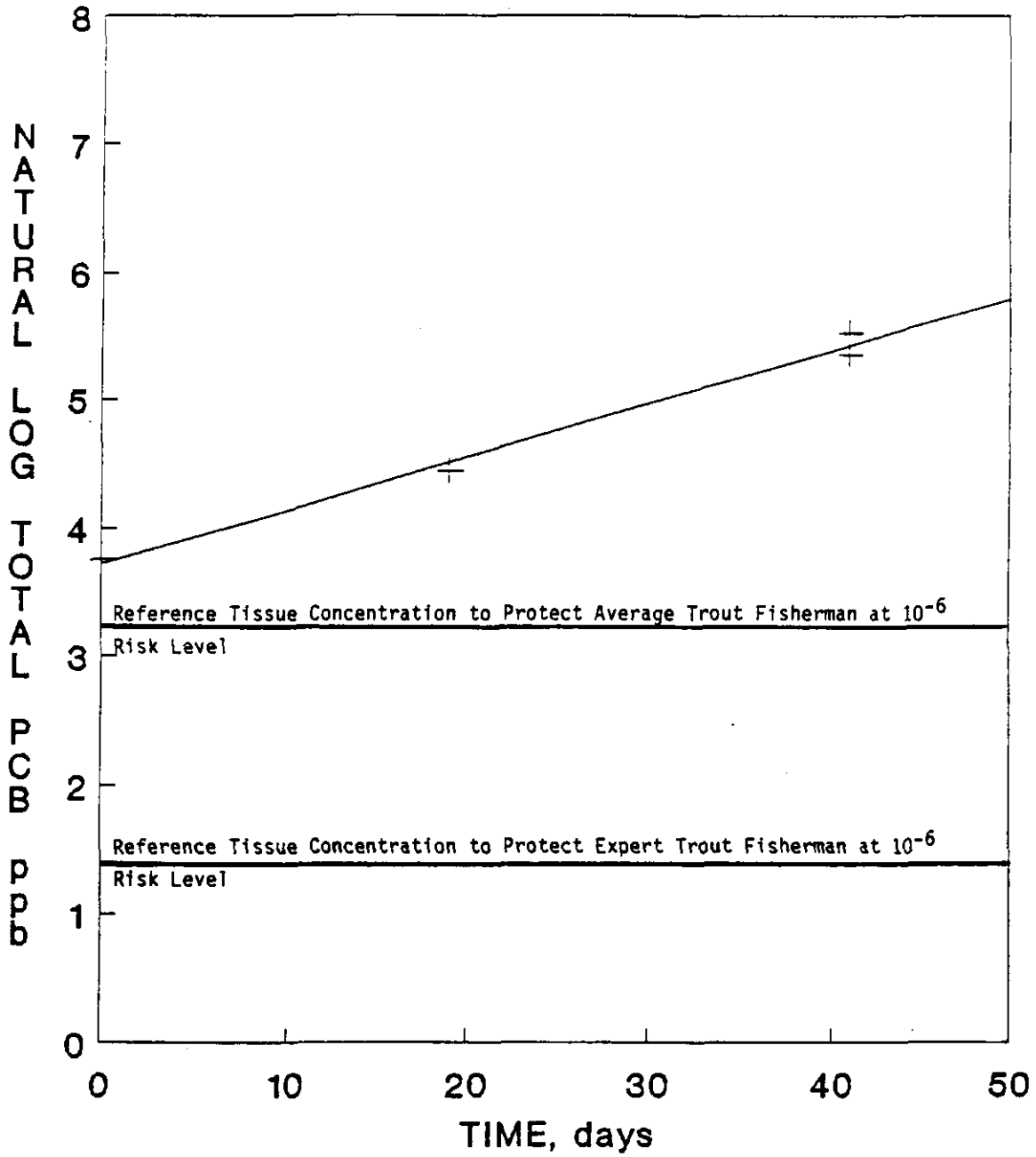


FIGURE 4

PCB 1260 IN BROWN TROUT
RED CLAY CREEK

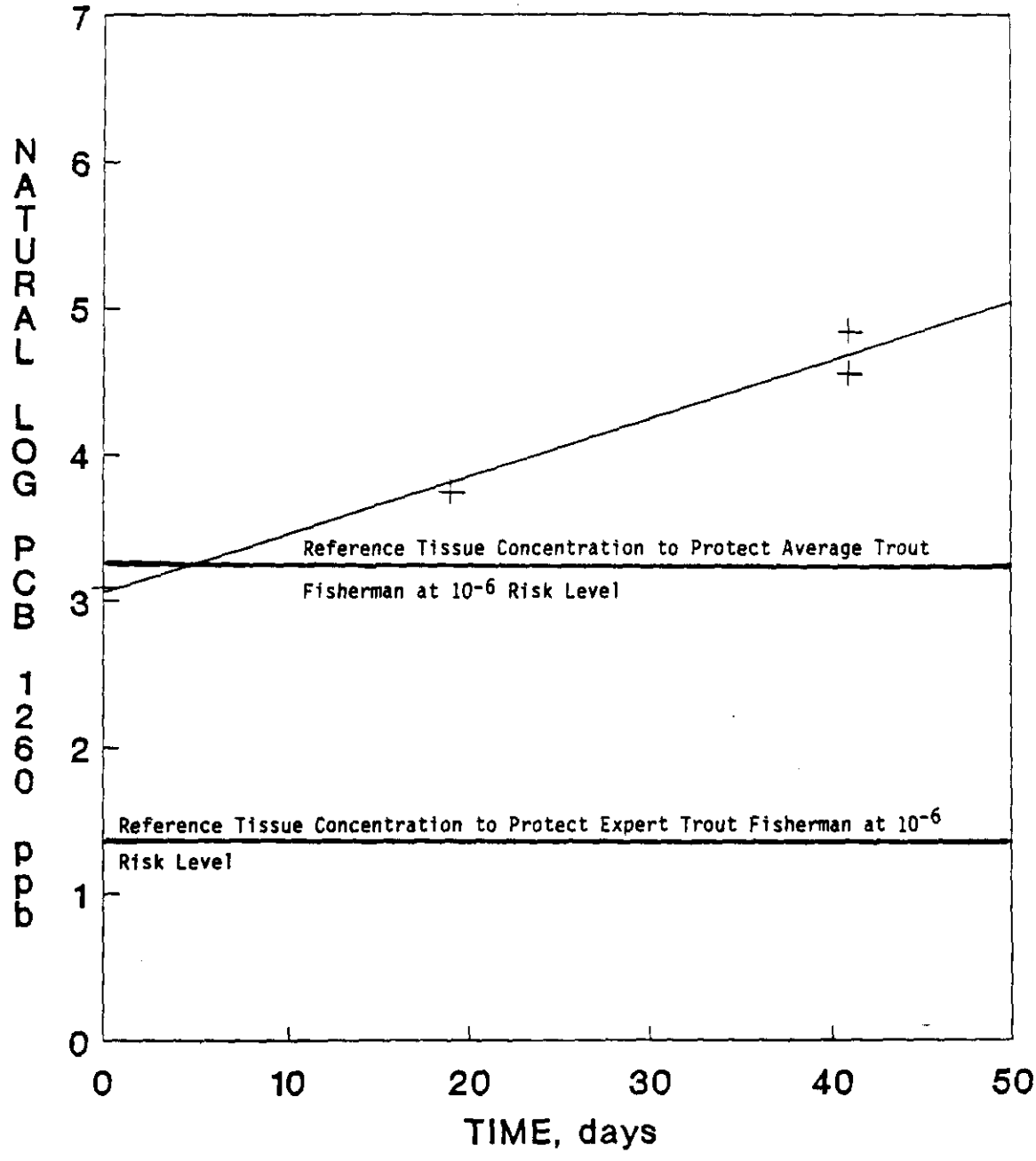


FIGURE 5

DDT UPTAKE IN BROWN TROUT
RED CLAY CREEK

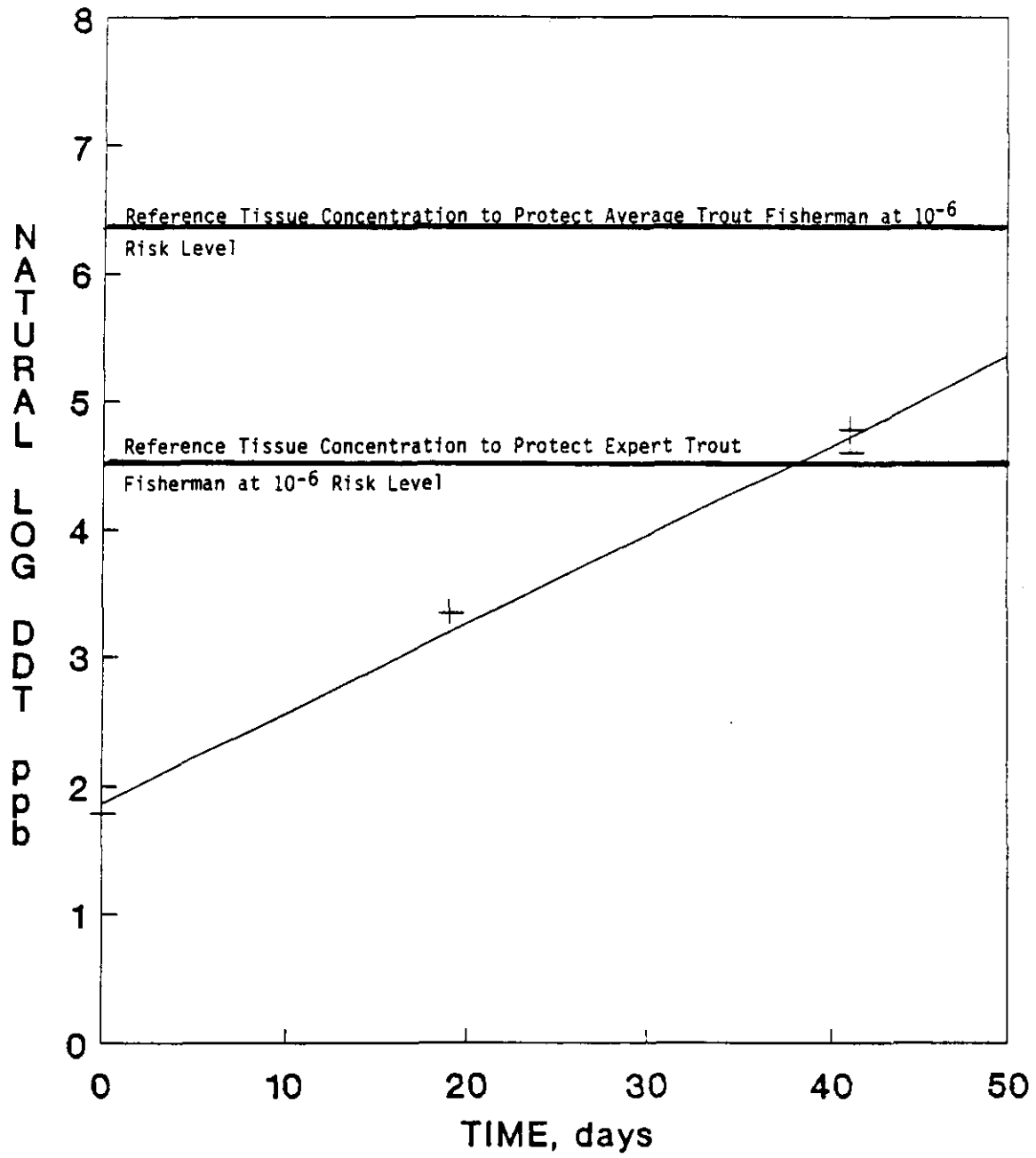


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FIGURE 6

DDD UPTAKE IN BROWN TROUT
RED CLAY CREEK

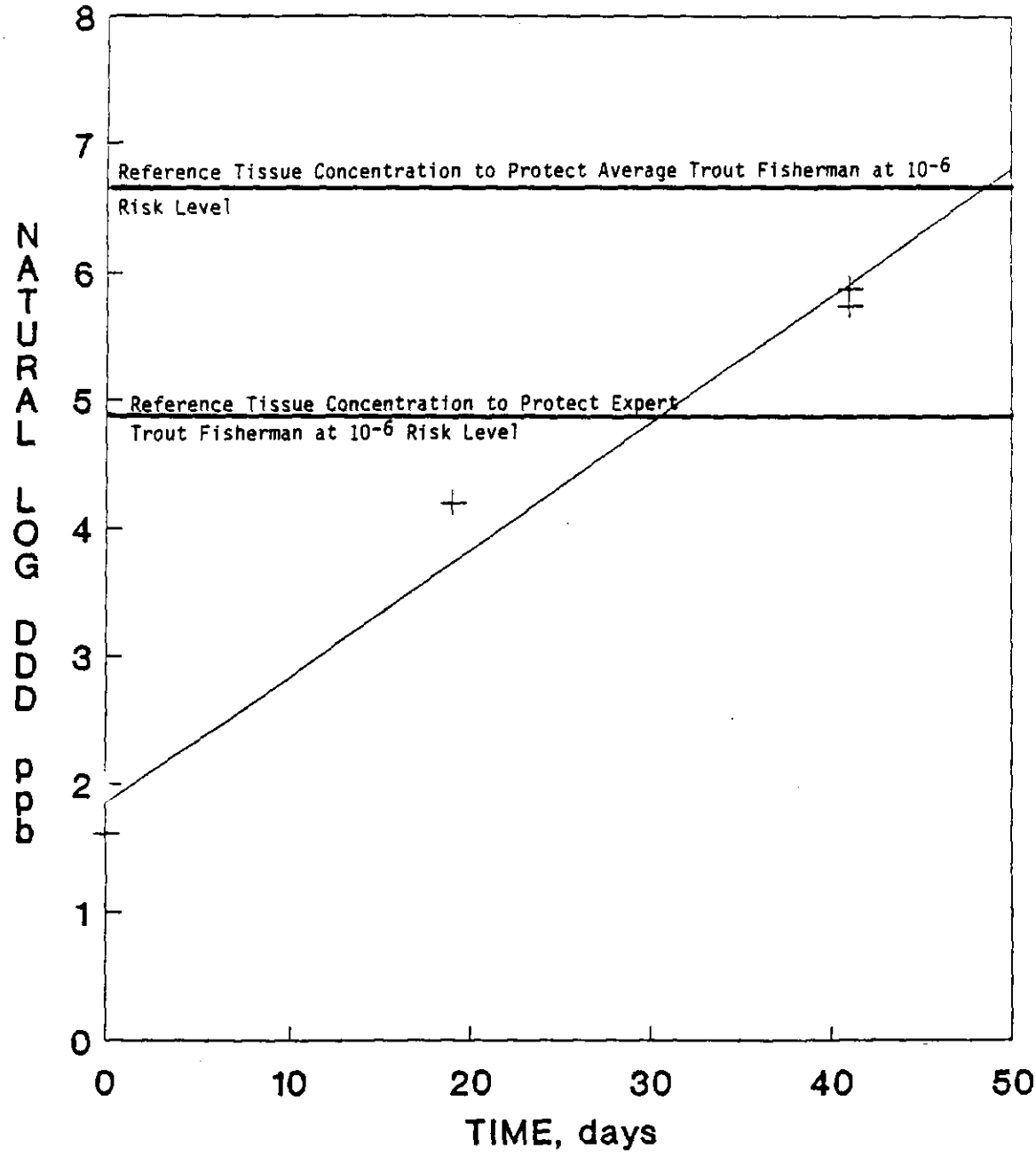


FIGURE 7

DDE UPTAKE IN BROWN TROUT
RED CLAY CREEK

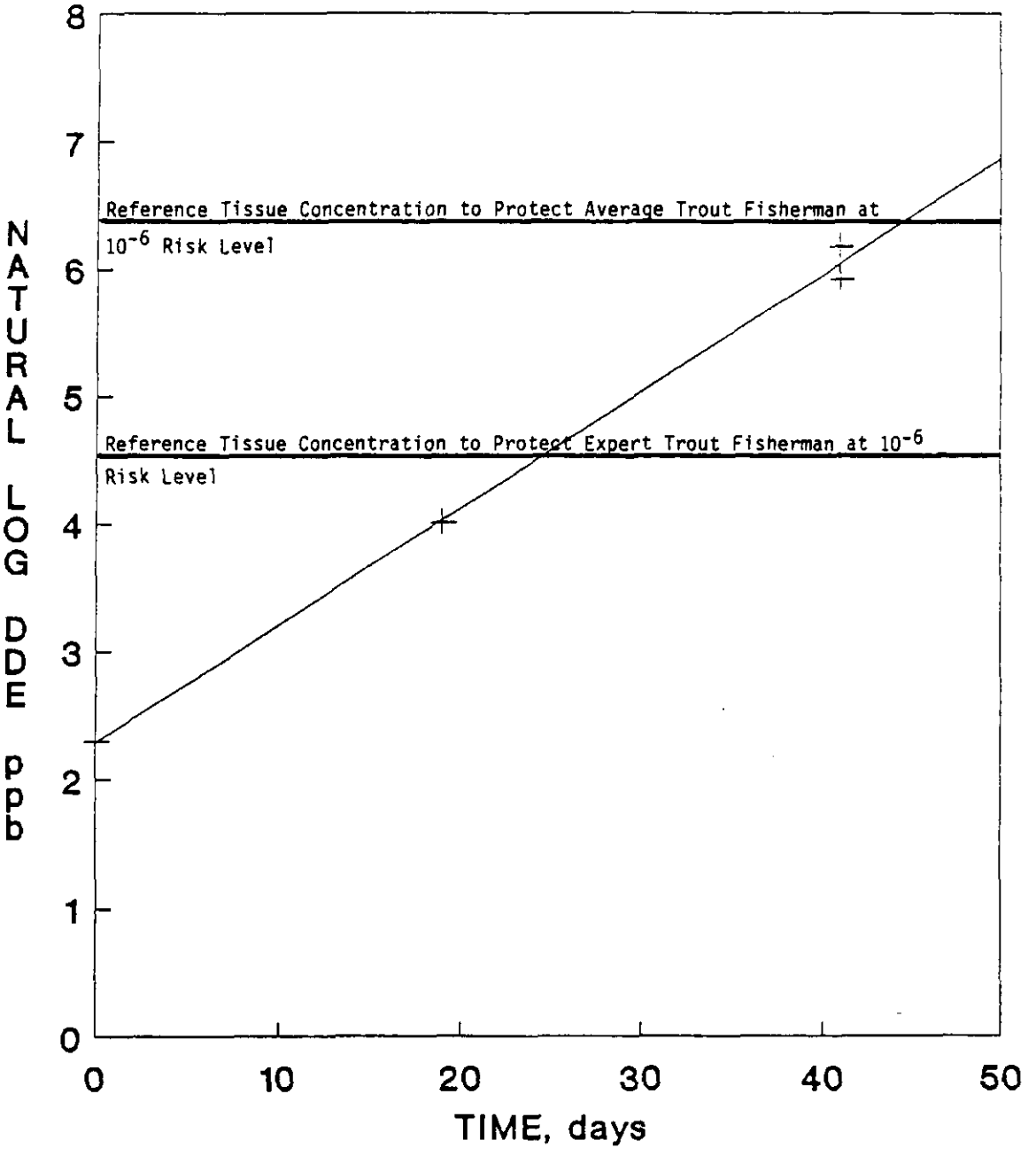
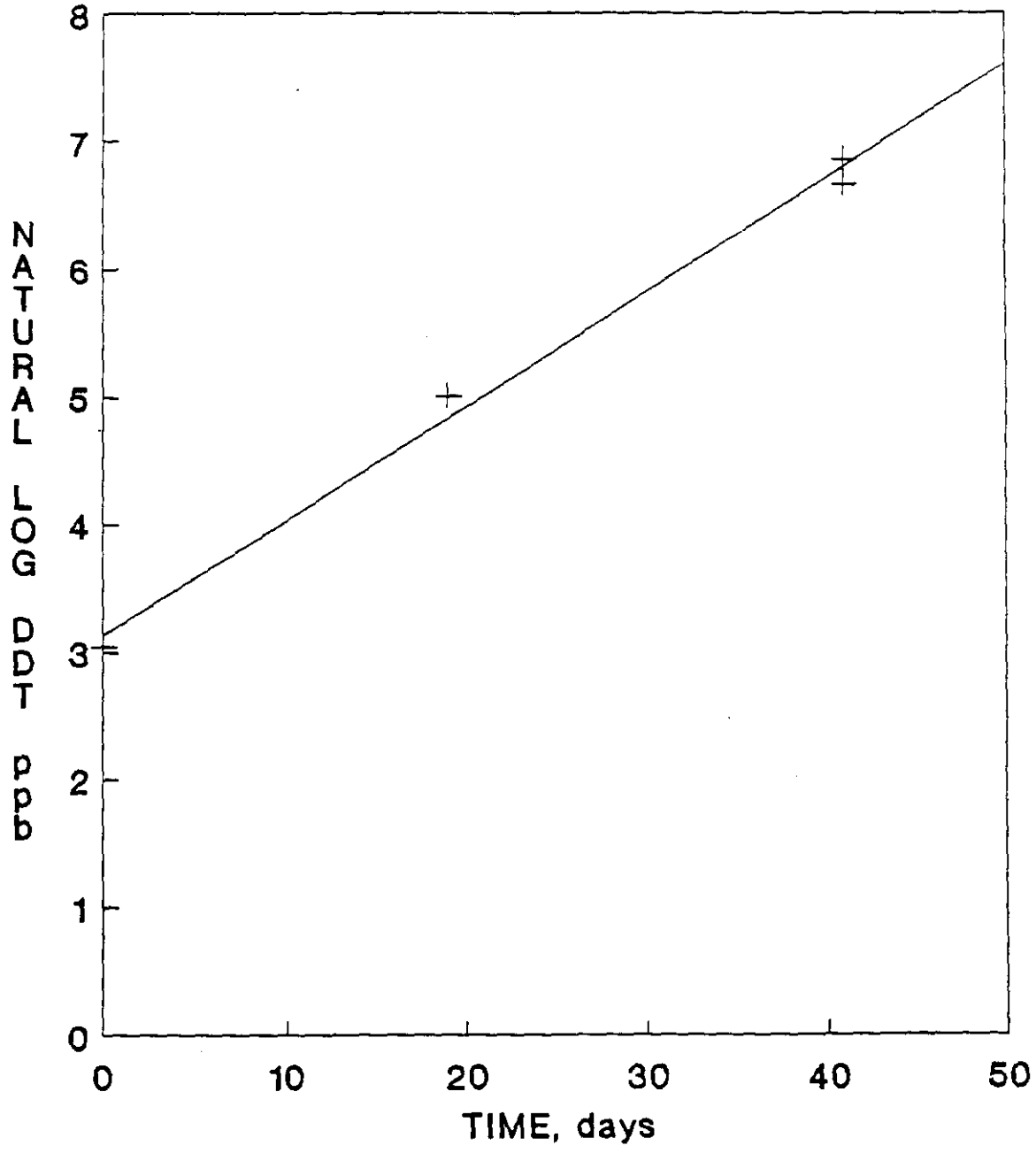


FIGURE 8

TOTAL DDT UPTAKE IN BROWN TROUT
RED CLAY CREEK



TOTAL DDT=DDT+DDD+DDE

FIGURE 9

DIELDRIN UPTAKE IN BROWN TROUT
RED CLAY CREEK

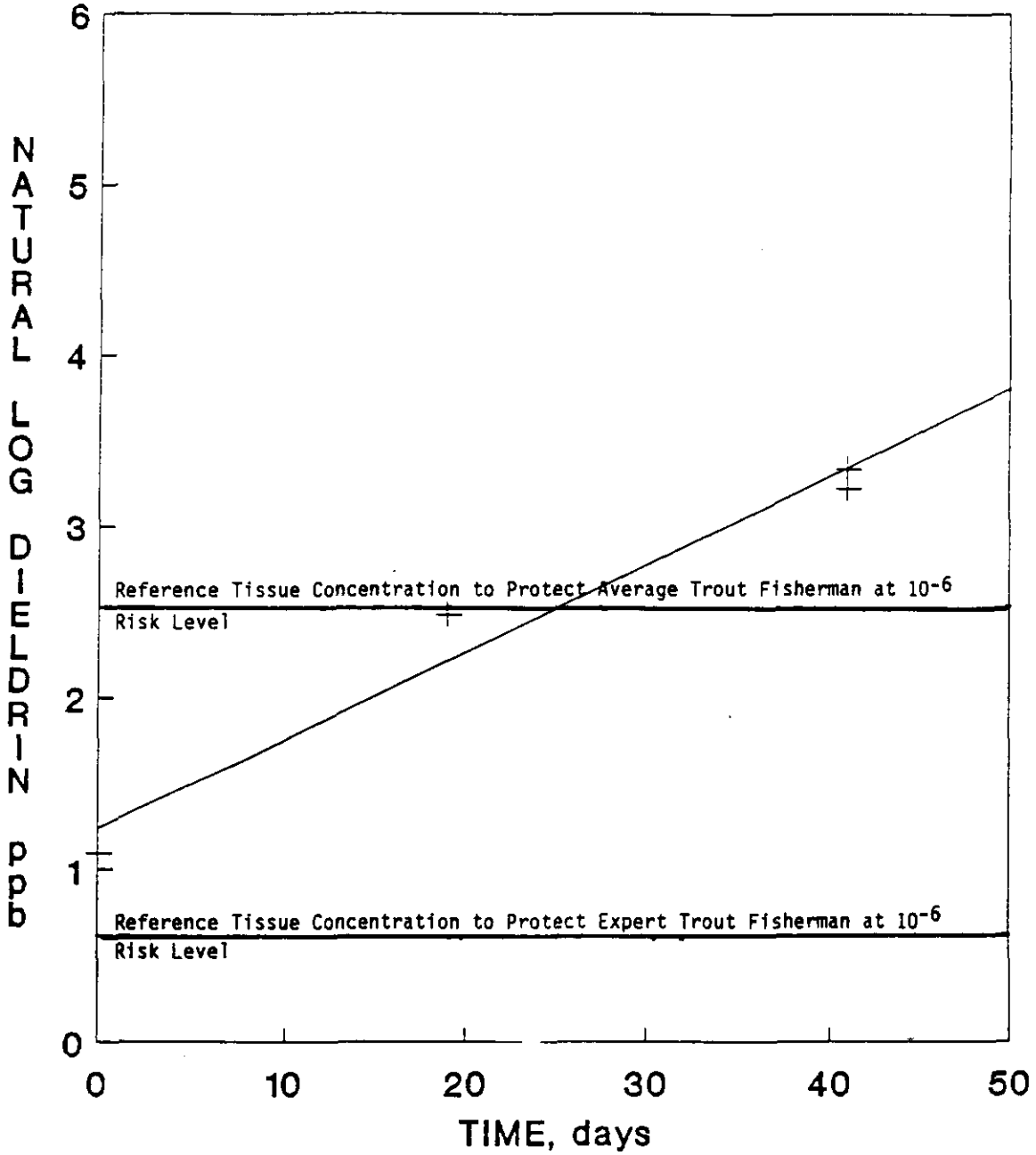


FIGURE 10

TOTAL NONACHLOR UPTAKE IN BROWN TROUT
RED CLAY CREEK

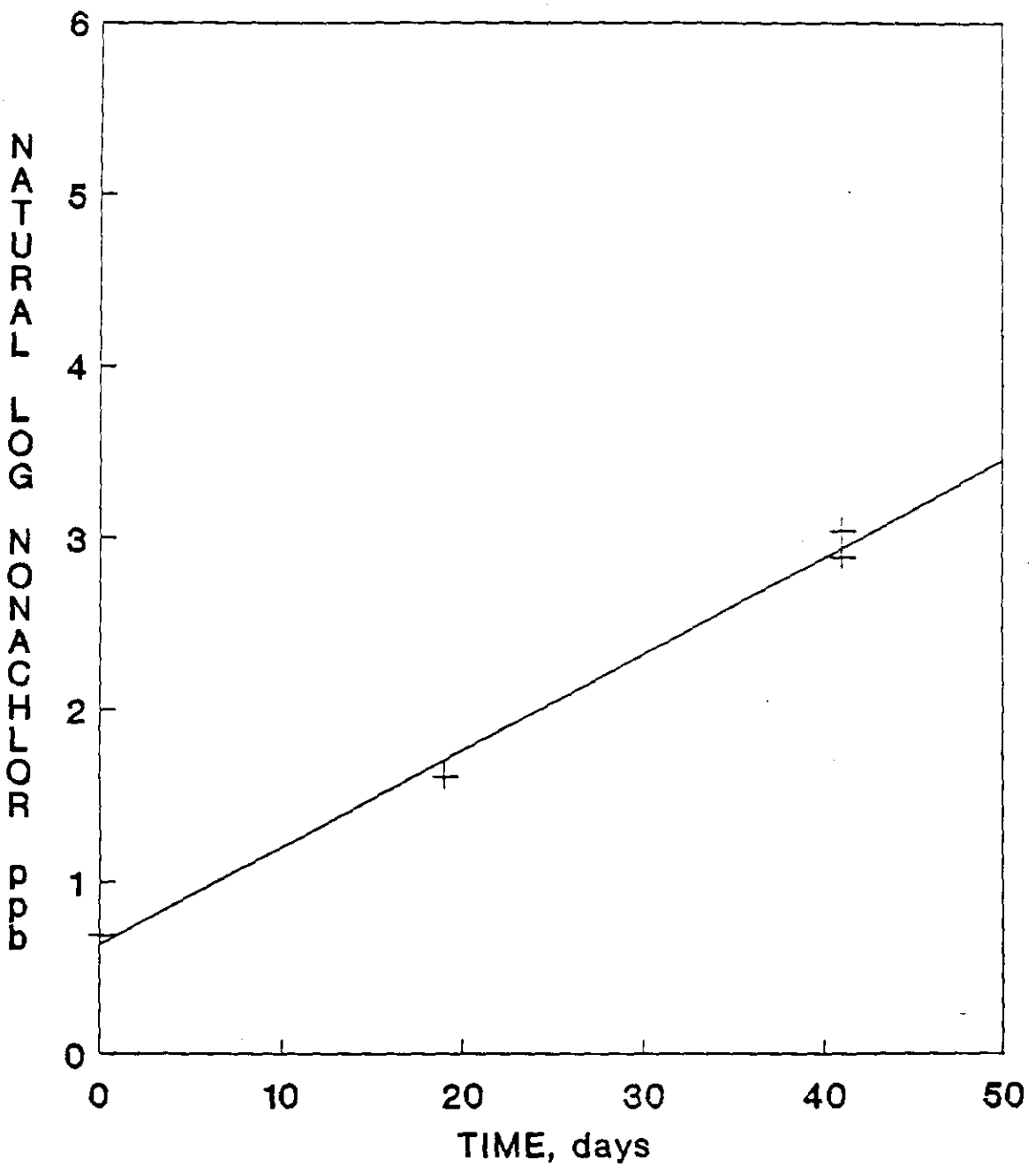


TABLE 1
LENGTHS AND WEIGHTS OF TROUT SAMPLES

Date Sample	Average Length, (cm)	Average Weight, (gm)
April 18, 1991	23.7	150.3
May 7, 1991	23.8	141.3
May 29, 1991	26.0	197.0
May 29, 1991	24.5	170.4

TABLE 2
RESULTS OF 1991 RED CLAY CREEK KINETIC UPTAKE STUDY
PCBs AND ORGANOCHLORINE PESTICIDES

Contaminant	Concentration (ppb) of Contaminant at Specified Time Past Stocking 0 days	19 days	41 days
Aroclor 1260 with 1254	43	85	250 210 (dup)
Aroclor 1260	22	42	95 126 (dup)
o,p DDT	4	12	41 33 (dup)
p,p DDT	2	16	78 66 (dup)
Total DDT	6	28	119 99 (dup)
o,p DDD	0	23	84 72 (dup)
p,p DDD	5	43	270 240 (dup)
Total DDD	5	66	354 312 (dup)
o,p DDE	2	6	28 30 (dup)
p,p DDE	8	49	450 340 (dup)
Total DDE	10	55	478 370 (dup)
Total DDT + DDD + DDE	21	149	951 781 (dup)
Dieldrin	3	12	25 28 (dup)
Aldrin	ND	ND	ND ND (dup)
alpha - BHC	ND	ND	ND ND (dup)
gamma - BHC	ND	1	2 2 (dup)

cis - Chlordane	ND	1	5 4 (dup)
trans - Chlordane	ND	ND	4 4 (dup)
Total Chlordane	ND	1	9 8 (dup)
Endrin	ND	ND	ND ND (dup)
Methoxychlor	ND	ND	ND ND (dup)
cis - Nonachlor	ND	2	11 10 (dup)
trans - Nonchlor	2	3	10 8 (dup)
Total Nonachlor	2	5	21 18 (dup)
Hexachlorobenzene	ND	1	3 2 (dup)
Lead	140	210	130 140 (dup)
Percent Lipid	4.4	3.3	3.7 3.3 (dup)

Notes:

1. dup = duplicate sample
2. ND = none detected

TABLE 3
RESULTS OF 1991 RED CLAY CREEK KINETIC UPTAKE STUDY
DIOXINS AND FURANS

Contaminant	Concentration (pptr) of Contaminant at Specified Time Past Stocking 0 days	19 days	41 days
2,3,7,8 - TCDD	0.11 (EMPC)	0.18	0.17 ND@0.2 (dup)
1,2,3,7,8 - PeCDD	ND	ND	0.17 (EMPC) 0.34 (EMPC), (dup)
1,2,3,4,7,8 - HxCDD	ND	ND	ND ND (dup)
1,2,3,6,7,8 - HxCDD	ND	ND	0.21 0.27 (EMPC), (dup)
1,2,3,7,8,9 - HxCDD	ND	ND	ND ND
1,2,3,4,6,7,8 - HpCDD	0.43 (EMPC),(B)	0.46 (B)	0.81 (B) 1.0 (B)
OCDD	12.5 (B)	2.6(B)	4.1 (B) 4.7 (B)
2,3,7,8 - TCDF	0.51 (EMPC),(B)	1.2 (B)	2.5 (B) 2.9 (B), (dup)
1,2,3,7,8 - PeCDF	ND	ND	ND ND (dup)
2,3,4,7,8 - PeCDF	ND	0.12	0.29 (EMPC) 0.28 (EMPC),(dup)
1,2,3,4,7,8 - HxCDF	ND	ND	ND ND (dup)
1,2,3,6,7,8 - HxCDF	ND	ND	0.05 (EMPC) ND@0.2 (dup)
2,3,4,6,7,8 - HxCDF	0.12 (EMPC),(B)	ND	ND@0.2 0.19 (EMPC),(dup)
1,2,3,7,8,9 - HxCDF	ND	ND	ND ND (dup)
1,2,3,4,6,7,8 - HpCDF	ND	ND	0.16 ND@0.3 (dup)
1,2,3,4,7,8,9 - HpCDF	ND	ND	ND ND (dup)

OCDF	1.4 (B)	0.51 (B)	ND ND (dup)
Total TCDD	0.18 (EMPC)	0.18	0.56 (EMPC) ND@0.2 (dup)
Total PeCDD	0.37 (EMPC)	0.38 (EMPC)	1.1 (EMPC) 0.34 (EMPC),(dup)
Total HxCDD	0.38 (EMPC)	ND	0.25 0.33 (EMPC),(dup)
Total HpCDD	0.80 (EMPC)	0.46	0.81 1.0 (dup)
Total TCDF	0.51 (EMPC)	1.8 2.4 (EMPC)	3.1 3.9
Total PeCDF	ND	0.12	0.10 0.28 (EMPC),(dup)
Total HxCDF	0.12 (EMPC)	ND	0.21 0.37 (EMPC),(dup)
Total HpCDF	ND	ND	0.20 ND@0.3 (dup)

Notes:

1. DD = Dibenzodioxin; DF = Dibenzofuran; TC = Tetrachloro; PeC = Pentachloro; HxC = Hexachloro; HpC = Heptachloro; and OC = Octachloro
2. EMPC = estimated maximum possible concentration
3. B = analyte found in lab blank as well as in field sample
4. ND = none detected
5. dup = duplicate result

TABLE 4
DIOXIN AND FURAN CONCENTRATIONS ADJUSTED
FOR BLANK CONTAMINATION

Contaminant	Concentration (pptr) of Contaminant at Adjusted for Blank Contamination 0 days	19 days	41 days
1,2,3,4,6,7,8 - HpCDD	0.28 (EMPC)	0.31	0.66 0.85 (dup)
OCDD	9.3	0	0.9 1.5 (dup)
2,3,7,8 - TCDF	0.43 (EMPC)	1.12	2.42 2.82 (dup)
2,3,4,6,7,8 - HxCDF	0.03 (EMPC)	ND	ND@0.02 0.1 (dup)
OCDF	0.75	0	ND ND (dup)

TABLE 5

REGRESSION EQUATIONS FOR OBSERVED CONTAMINANT UPTAKE

Contaminant	$\ln C_B(t) = \ln C_{Bo} + (k_1/K_B)t$	Correlation Coefficient
Aroclor 1260 w/1254	y = 3.725 + 4.131E - 02x	0.995
Aroclor 1260	y = 3.054 + 3.964E - 02x	0.988
o,p DDT	y = 1.413 + 5.374E - 02x	0.996
p,p DDT	y = 0.8548 + 8.508E - 02x	0.992
Total DDT	y = 1.868 + 6.956E - 02x	0.996
o,p DDD	y = 0.4300 + 0.1002x	0.964
p,p DDD	y = 1.737 + 9.409E - 02x	0.996
Total DDD	y = 1.854 + 9.897E - 02x	0.987
o,p DDE	y = 0.6392 + 6.596E - 02x	0.998
p,p DDE	y = 2.083 + 9.482E - 02x	0.998
Total DDE	y = 2.292 + 9.134E - 02x	0.998
Total DDT + DDD + DDE	y = 3.136 + 8.933E - 02x	0.997
Dieldrin	y = 1.244 + 5.109E - 02x	0.983
Aldrin	No uptake observed	--
alpha-BHC	No uptake observed	--
gamma-BHC	Uptake observed, but no equation confidently produced	--
cis-Chlordane	Uptake observed, but no equation confidently produced	--
trans-Chlordane	Uptake observed, but no equation confidently produced	--
Total Chlordane	Uptake observed, but no equation confidently produced	--
Endrin	No uptake observed	--
Methoxychlor	No uptake observed	

cis-Nonachlor	y = -0.1522 + 5.943E - 02x	0.986
trans-Nonachlor	y = 0.5821 + 3.807E - 02x	0.976
Total Nonachlor	y = 0.6402 + 5.621E - 02x	0.997
Hexachlorobenzene	Uptake observed, but no equation possible	--
Dioxins and Furans	No equation confidently produced	--

TABLE 6
OCTANOL/WATER PARTITION COEFFICIENTS (Log P) AND BIOCONCENTRATION FACTORS (K_B)

Contaminant	Octanol/Water Partition Coefficient			Bioconcentration Factor		
	Log P	Reference	Comment	Log k_B	Reference	Comment
Aroclor 1260 with 1254	5.37	Mackay [7]	Listed value is average between Aroclor 1260 and 1254	3.53	EPA [5]	
Aroclor 1260	5.59	Mackay [7]		3.71	"	
o,p - DDT	6.91	CLOGP [8]		4.75	"	
p,p - DDT	6.91	"		4.75	"	
Total DDT	6.91	"		4.75	"	
o,p - DDD	6.21	"		4.20	"	
p,p - DDD	6.21	"		4.20	"	
Total DDD	6.21	"		4.20	"	
o,p - DDE	6.94	"		4.77	"	
p,p - DDE	6.94	"		4.77	"	
Total DDE	6.94	"		4.77	"	
Total (DDT + DDD + DDE)	6.69	"		4.58	"	
Dieldrin	2.92	"		1.60	"	

TABLE 7

ESTIMATED UPTAKE RATE CONSTANTS (k_1)

Contaminant	k_1 (day^{-1})	Comment
Aroclor 1260 with 1254	140	
Aroclor 1260	203	Compares closely to a value of 332 day^{-1} as reported in Mackay [7]
o,p - DDT	3020	
p,p - DDT	4780	
Total DDT	3910	
o,p - DDD	1590	
p,p - DDD	1490	
Total DDD	1570	
o,p - DDE	3880	
p,p - DDE	5580	
Total DDE	5380	
Total DDT + DDD + DDE	3400	
Dieldrin	2	

APPENDIX A

ESTIMATION OF REFERENCE TISSUE CONCENTRATIONS

GOVERNING EQUATIONS

Elevated levels of toxic substances in fish may cause adverse health effects in human consumers. Health effects are grouped into two broad categories: carcinogenic effects and noncarcinogenic effects. Some chemicals may cause both types of effects.

It is possible to estimate the concentration of a contaminant in fish that is associated with some acceptably small, prespecified risk level. Section A below presents an equation which can be used to estimate "acceptable" or "reference" tissue concentrations for carcinogenic compounds in fish. Section B below presents an equation which can be used to estimate "acceptable" tissue concentrations for systemic (noncarcinogenic) compounds in fish. These equations have been adapted from and are consistent with EPA guidance [5, 9, 11].

A. Carcinogenic Effects

(1A)

$$\text{reference tissue concentration (ppm)} = \frac{(RL)(BW)\,[LT \times (365\ \text{days/yr})]}{(q_1^*)[CR \times (1\ \text{kg}/1000\ \text{gm})][ED\ (365\ \text{days/yr})](DF)}$$

where: RL = risk level, 10^{-x}, (set equal to 10^{-6})
BW = weight of average human adult, (kg)
LT = average lifetime duration, (years)
q_1^* = cancer potency slope, $(\text{mg/kg/day})^{-1}$
CR = human consumption rate of fish, (gm/day)
ED = exposure duration (years)
DF = diet fraction

B. Noncarcinogenic Effects

(2A)

$$\text{reference tissue concentration} = \frac{(RfD)(BW)\,[LT \times (365\ \text{days/yr})]}{[CR \times (1\ \text{kg}/1000\ \text{gm})][ED \times (365\ \text{days/yr})](DF)}$$

where: RfD = reference dose, (mg/kg/day)
BW, LT, CR, ED, and DF as above

CANCER POTENCY SLOPES AND REFERENCE DOSES

A. Cancer Potency Slopes

Values of q_1*, the cancer potency slope, were obtained from the U. S. EPA's Integrated Risk Information System (IRIS) database [9]. Potency slopes for contaminants detected in this study are listed in Table A1 of this Attachment. Selected excerpts from the individual chemical files within IRIS appear as Attachment B of this report. Note the weight of evidence classification "B2" for all pollutants of concern. This indicates that these pollutants are probable human carcinogens based upon sufficient evidence of carcinogenicity in laboratory animals but insufficient evidence of cancer in humans.

B. References Doses

RfD values were also obtained from the IRIS database. Of the chemicals considered in the Kinetic Uptake Study, only DDT and Dieldrin were found to have RfDs within IRIS. Those RfDs appear in Table A1 along with the potency slopes.

EXPOSURE FACTORS

The variables BW, LT, CR, ED, and DF in Equations (1A) and (2A) are referred to as exposure factors. For the purpose of this report, BW, LT, ED, and DF have been assigned constant values of 70 kg, 75 years, 30 years, and 0.2 respectively. These values are consistent with recommendations within the U. S. EPA's "Exposure Factor Handbook" [10]. Because there are certain professional judgements that enter into selection of values for ED and DF, an analysis of the sensitivity of those two variables to computed reference tissue concentrations is presented later in this Appendix.

The fish consumption habits of trout fishermen in Delaware are believed to differ from national average fish consumption habits applicable to the entire U. S. population. Because of this, site-specific consumption rates (CR values) have been derived for purposes of this study. This derivation is presented below.

TROUT CONSUMPTION RATES

Reasonable estimates of trout consumption can be obtained through knowledge of creel limits, length of fishing season, stocking frequency, and size of fish stocked. Because we might expect trout consumption to vary considerably from angler to angler, this section attempts to develop a range of plausible consumption rates. The range considered varies from the reasonable worst case (expert fisherman) down to the casual participate or family member.

The assumptions used to develop trout consumption rates are presented below [12].

- Fishing pressure occurs primarily over a one-month period;
- Fish are stocked in four waves, one wave per week;

- Daily creel limit is six fish;
- The expert fisherman captures the creel limit on the day of and day after each stocking wave and captures two fish all other days of the season;
- The expert fisherman consumes all of his catch;
- The average weight of the fish on a whole body basis is 0.4 pounds (equal to 6.4 ounces or 181.4 grams);
- The edible portion of the fish is approximately two-thirds of the whole fish. This results in an edible portion of 0.267 pounds per fish (or 4.3 ounces or 121 grams).

Using the first and fourth assumptions, the total number of trout the expert fisherman catches per season can be computed as 88. Averaged over the one-month effective season, this represents 2.93 fish per day, or roughly three fish per day. On an annual basis, consumption of 88 fish represents 0.24 fish per day. The daily consumption taken over a year then becomes:

$$0.24 \frac{\text{fish}}{\text{day}} \times \frac{121 \text{ grams}}{\text{fish}} = 29 \frac{\text{grams}}{\text{day}}$$

Other plausible consumption rates can be computed by assuming the fisherman retains an average of 2, 1, or 0.5 fish per day during the season. The consumption rates corresponding to these catch frequencies are 18.6 grams per day, 9.3 grams per day, and 4.6 grams per day, respectively. For lack of firm data, this last consumption rate was taken as the average trout consumption rate for the hypothetical "at risk" population. This assumption is not inconsistent with the general observation that mean consumption rates are typically within a single order or magnitude of a reasonable worst case consumption rate (say, the 95th percentile).

ESTIMATION OF REFERENCE TISSUE CONCENTRATIONS

Reference tissue concentrations were computed using Equation (1A) for probable human carcinogenic effects and Equation (2A) for systemic human health effects. Table A2 presents results for the probable carcinogens. Table A3 presents the results for systemic effects. Note that the units of the reference tissue concentrations in Table A2 are parts per billion (ppb) and that the corresponding units in Table A3 are in units of parts per million (ppm). Note further that the reference tissue concentrations associated carcinogenic effects of DDT and dieldrin are significantly more stringent than the reference tissue concentrations associated with systemic effects for those same two pollutants. In short, the carcinogenic effect is more critical.

Note also from Tables A2 and A3 that two separate consumption rates were considered to correspond to the expert trout fisherman (29 g/d) and the average trout fisherman (4.6 g/d). Note also that reference tissue concentrations associated with two cancer risk levels, 10^{-6} and 10^{-5}, are presented in Table A2. Although reference tissue concentrations are presented for the two different risk

levels, only the concentrations associated with the 10^{-6} level were used for purposes of comparison against the uptake data. This was felt to be appropriate since both Pennsylvania and Delaware regulate probable human carcinogens in water at the 10^{-6} risk level [13, 14]. Cross media consistency between water and fish tissue argues for such an approach. One final point is in order. Note that prior to plotting the applicable reference tissue concentrations on Figures 3 through 10, the natural logarithm of each value was taken to ensure consistency of scale within those figures.

As a related matter, readers may question why U. S. Food and Drug Administration (FDA) action levels were not used as reference tissue concentrations. Several reasons are offered. First, the FDA, in accordance with its legislative mandate, is primarily responsible for regulating risks in foods sold in interstate commerce [15]. Clearly, trout taken from the Red Clay Creek are not a part of an interstate commercial fishery. Second, because the FDA focuses on major interstate commercial fisheries, the assumptions they use in deriving their action levels need to and do reflect expected consumption habits of the general population that purchases fish sold in the interstate marketplace. Since fish sold in interstate commerce comes from many waterbodies, the likelihood that an average consumer will be steadily exposed to fish taken from a particular contaminated waterbody is substantially reduced. The result is that the action level is, in effect, increased in response to this "diluting" effect. The implication to the local sports angler is that the FDA action level is not likely to be protective if that person consumes more than a few meals per year from a particular contaminated waterbody.

The third reason to reject FDA action levels in situations involving recreational fisheries is that the action levels reflect judgements regarding economic impacts to commercial fishermen. The effect of this consideration is also to increase the action level. Again, however, since we are not dealing with a commercial fishery in the case of Red Clay Creek trout, it would be inappropriate to consider economic impact to commercial fishermen. Notwithstanding this point, a legitimate argument could be made that economic considerations should not, as a matter of public policy, be cloaked in a number that the general public believes to be based solely on health risk considerations.

To summarize, to embrace the FDA action levels is to accept all the underlying scientific and economic assumptions. To the extent those assumptions are not applicable or, at the least, are questionable, argues for alternative methods which are scientifically supportable. Although considerable scientific uncertainty exists in the alternative method presented in this report, it nevertheless represents a more cautious approach than reliance on FDA action levels.

SENSITIVITY ANALYSIS

Professional judgement is involved in the selection of the exposure factors ED (exposure duration) and DF (diet fraction). The baseline values selected in this study were 30 years and 0.2, respectively. However, alternative values could have been legitimately selected. Values for ED, which represents the length of time a person is likely to live in one area, could have been specified over a range from 9 years up to 75 years. Similarly, values of DF, which

represent the fraction of all fish a person consumes from a particular waterbody, could have been specified over a range from near zero up to 1.0. The range considered in this sensitivity analysis is 0.2, which is considered typical [11], to 1.0, which is equivalent to saying that all of one's fish intake is from the contaminated waterbody.

To investigate the influence of these variables on the computed reference tissue concentrations, a simple sensitivity analysis was performed. This involved holding all values in Equation (1A) constant except ED and DF, systematically varying ED and DF between the range noted above, and recomputing reference tissue concentrations. The results of this exercise are summarized in Table A4. All values assume a 10^{-6} cancer risk level. The column labelled "most conservative" assumes the longest exposure duration (e.g. 75 yrs.) and the largest diet fraction (e.g. 1.0). The column labelled "least conservative" assumes the shortest exposure duration (e.g. 9 yrs.) and the smallest practical diet fraction (e.g. 0.2). The column labelled "baseline scenario" assumes an exposure duration of 30 years and a diet fraction of 0.2.

UNCERTAINTIES

The scientific knowledge concerning adverse health effects of toxic pollutants on humans is incomplete. Consequently, uncertainty exists in assessing human health risks associated with chemical exposure. Among the sources of uncertainty which are inherent in the reference tissue concentrations presented in Tables A2 and A3 include the following:

- Use of dose-response data from laboratory experiments conducted on genetically homogeneous animal populations as surrogates for a heterogeneous human population of widely varying sensitivity (i.e. interspecies extrapolation);
- Extrapolation of data from high dose, acute or subchronic animal studies to low dose, chronic human exposures (i.e. low dose extrapolation);
- Lack of consideration of adsorption, distribution, and excretion of toxic chemicals on overall toxic response (i.e. "blackbox" assumption);
- Use of single chemical, single route of exposure animal tests which do not consider possible synergistic or antagonistic responses which can result from multiple chemical exposures, through multiple routes;
- Use of point estimates of exposure factors such as fish consumption rate, diet fraction, exposure duration, body weight, and lifetime duration; and
- In the case of PCBs, use of Aroclor equivalents as an accurate reflection of actual PCB content.

Although all of the factors listed above are arguably significant, the first and second factors are perhaps the most important within the realm of "regulatory" toxicology and risk assessment. Many lay persons and scientists alike reject the notion that laboratory animals are good surrogates of humans. However, the vast majority of scientists do consider animal data to be essential in the risk assessment process if for no other reason than the fact that the

human data is sparse or nonexistent. Another factor that tends to blunt criticism of interspecies extrapolation is that animal data may over- or understate health effects in the human population, thereby eliminating any solid basis to claim that animal data categorically overstates risk to humans.

Extrapolation from high dose to low dose introduces the greatest uncertainty in the computed reference tissue concentrations. The cancer potency slopes appearing within Table A2 are based on a linearized multi-stage dose-response model. This model is generally believed to provide conservative estimates of cancer risk at low doses. The implication to the computed reference tissue concentrations is that they may be more stringent (i.e. numerically smaller) than necessary to protect the consumer at the specified risk level. In other words, significantly higher pollutant concentrations in the fish may, in reality, be "safe." However, prudent regulatory policy is to treat uncertainties conservatively as opposed to permissively. This is especially important when dealing with health effects as serious as cancer.

TABLE A1

TOXICOLOGICAL PROPERTIES OF AROCLORS AND CHLORINATED PESTICIDES

A. Carcinogenic Effects

Pollutant	Cancer Slope Factor, q*, $(mg/kg/day)^{-1}$	Critical Effect in Experimental Animals	Evidence of Cancer in Humans	Weight-of-Evidence Classification	Reference
Aroclor 1260	7.7	Hepatocellular carcinomas in rodents	Inadequate, yet suggestive	B2, probable human carcinogen	IRIS [9]
Aroclor 1254	Not Available	--	--	--	--
DDT	0.34	Liver tumors in rodents	Inadequate	B2, probable human carcinogen	IRIS [9]
DDD	0.24	Liver, lung, and thyroid tumors in rodents	None	B2, probable human carcinogen	IRIS [9]
DDE	0.34	Liver and thyroid tumors in rodents	Inadequate	B2, probable human carcinogen	IRIS [9]
Dieldrin	16	Liver tumors, hepatocarcinomas, and pulmonary metastases in rodents	Inadequate	B2, probable human carcinogen	IRIS [9]
Nonachlor	Not Available	--	--	--	--

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B. Noncarcinogenic Effects

DDT and Dieldrin have been shown to exhibit noncarcinogenic health effects in laboratory animals. The reference dose reported in IRIS for DDT is 5E-4 mg/kg/day, based on a No Observed Effect Concentration (NOEC) of 1 ppm in rats fed DDT in a 27-week study. The reference dose reported in IRIS for Dieldrin is 5E-5 mg/kg/day, based on a NOEC of 0.1 ppm in rats fed Dieldrin in a 2-year study.

TABLE A2
SUMMARY OF EXPOSURE, POTENCY, AND CORRESPONDING REFERENCE TISSUE CONCENTRATIONS FOR PROBABLE HUMAN CARCINOGENS

	EXPOSURE FACTORS					RISK DETERMINATION			
Pollutant	Consumption Rate (g/d)	Exposure Duration (yrs)	Diet Fraction	Body Weight (kg)	Lifetime Duration (yrs)	Potency Slope $^{-1}$ (mg/kg/day)	Weight of Evidence	Risk Level	REFERENCE TISSUE CONCENTRATION (ppb)
PCB	4.6	30	0.2	70	75	7.7	B2	10^{-6}	25
	4.6	30	0.2	70	75	7.7	B2	10^{-5}	250
	29	30	0.2	70	75	7.7	B2	10^{-6}	3.9
	29	30	0.2	70	75	7.7	B2	10^{-5}	39
DDT	4.6	30	0.2	70	75	0.34	B2	10^{-6}	560
	4.6	30	0.2	70	75	0.34	B2	10^{-5}	5600
	29	30	0.2	70	75	0.34	B2	10^{-6}	89
	29	30	0.2	70	75	0.34	B2	10^{-5}	890
DDD	4.6	30	0.2	70	75	0.24	B2	10^{-6}	790
	4.6	30	0.2	70	75	0.24	B2	10^{-5}	7900
	29	30	0.2	70	75	0.24	B2	10^{-6}	130
	29	30	0.2	70	75	0.24	B2	10^{-5}	1300
DDE	4.6	30	0.2	70	75	0.34	B2	10^{-6}	560
	4.6	30	0.2	70	75	0.34	B2	10^{-5}	5600
	29	30	0.2	70	75	0.34	B2	10^{-6}	89
	29	30	0.2	70	75	0.34	B2	10^{-5}	890
Dieldrin	4.6	30	0.2	70	75	16	B2	10^{-6}	12
	4.6	30	0.2	70	75	16	B2	10^{-5}	120
	29	30	0.2	70	75	16	B2	10^{-6}	1.9
	29	30	0.2	70	75	16	B2	10^{-5}	19

TABLE A3

SUMMARY OF EXPOSURE, REFERENCE DOSE, AND CORRESPONDENCE REFERENCE TISSUE CONCENTRATIONS FOR SYSTEMIC TOXICANTS

	EXPOSURE FACTORS					REFERENCE DOSE		
Pollutant	Consumption Rate (g/d)	Exposure Duration (yrs)	Diet Fraction	Body Weight (kg)	Lifetime Duration (yrs)	Reference Dose (mg/kg/day)	Confidence	REFERENCE TISSUE CONCENTRATION (ppm)
DDT	4.6	30	0.2	70	75	5E-4	Medium	95
	29	30	0.2	70	75	5E-4	Medium	15
Dieldrin	4.6	30	0.2	70	75	5E-5	Medium	1.5
	29	30	0.2	70	75	5E-5	Medium	9.5

TABLE A4

INFLUENCE OF EXPOSURE DURATION AND DIET FRACTION ON REFERENCE TISSUE CONCENTRATIONS

Pollutant	Exposed Population	Reference Tissue Concentration, (ppb) Most Conservative	Baseline Condition	Least Conservative
PCB	Expert Fisherman	0.31	3.9	13
	Average Fisherman	2.0	25	82
DDT (and DDE)	Expert Fisherman	7.1	89	300
	Average Fisherman	45	560	1900
DDD	Expert Fisherman	10	130	420
	Average Fisherman	63	790	2600
Dieldrin	Expert Fisherman	0.2	1.9	6.3
	Average Fisherman	1.0	12	40

APPENDIX B

SELECTED EXCERPTS FROM THE U. S. EPA'S

INTEGRATED RISK INFORMATION SYSTEM DATABASE

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name: Polychlorinated biphenyls (PCBs)
CASRN: 1336-36-3

The Carcinogenicity Assessment Section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The Carcinogen Assessment Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to the Oral RfD and Inhalation RfC Sections for information on long-term toxic effects other than carcinogenicity.

EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification: B2; probable human carcinogen

BASIS

hepatocellular carcinomas in three strains of rats and two strains of mice and inadequate yet suggestive evidence of excess risk of liver cancer in humans by ingestion and inhalation or dermal contact.

HUMAN CARCINOGENICITY DATA

Inadequate. Although there are many studies, the data are inadequate due to confounding exposures or lack of exposure quantification. The first documentation of carcinogenicity associated with PCB exposure was reported at a New Jersey petrochemical plant involving 31 research and development employees and 41 refinery workers (Bahn et al., 1976, 1977). Although a statistically significant increase in malignant melanomas was reported, the two studies failed to report a quantified exposure level and to account for the presence of other potential or known carcinogens. In an expanded report of these studies, NIOSH (1977) concurred with the Bahn et al. (1976) findings. Brown and Jones (1981) reported a retrospective cohort mortality study on 2567 workers who had completed at least 3 months of employment at one or two capacitor manufacturing plants. Exposure levels were 24-393 mg/cu.m at plant A and 318-1260 mg/cu.m at plant B. No excess risk of cancer was observed. In a 7-year follow-up study, Brown (1987) reported a statistically significant excess risk of liver and biliary cancer, with four of the five liver cancers in female workers at plant B. A review of the pathology reports indicated that two of the liver tumors counted in the follow-up study were not primary liver tumors. When these tumors are excluded the elevation in incidence is not statistically significant. The results also may be confounded by population differences in

:ohol consumption, dietary habits, and ethnic composition.

Bertazzi et al. (1987) conducted a mortality study of 544 male and 1556 female employees of a capacitor-making facility in Northern Italy. Aroclor 1254 and Pyralene 1476 were used in this plant until 1964. These were progressively replaced by Pyralenes 3010 and 3011 until 1970, after which lower chlorinated Pyralenes were used exclusively. In 1980 the use of PCBs was abandoned. Some employees also used trichloroethylene but, according to the authors, were presumed to be protected by efficient ventilation. Air samples were collected and analyzed for PCBs in 1954 and 1977 because of reports of chloracne in workers. Quantities of PCBs on workers' hands and workplace surfaces also were measured in 1977. In 18 samples, levels ranged from 0.2-159.0 ug/sq.m on workplace surfaces and 0.3-9.2 ug/sq.m on workers' hands.

The authors compared observed mortality with that expected between 1946 and 1982 based on national and local Italian mortality rates. With vital status ascertainment 99.5% complete, relatively few deaths were reported by 1982 [30 males (5.5%) and 34 females (2.2%)]. In cohort males, the number of deaths from malignant tumors was significantly higher than expected compared with local or national rates, as was the number of deaths from cancer of the GI tract (6 observed vs. 1.7 national expected and 2.2 local expected). Of the six GI cancer deaths, one was due to liver cancer and one to biliary tract cancer. Deaths from hematologic neoplasms in males were also higher than expected, but the excess was not statistically significant. Total cancer `ths in females were significantly elevated in comparison to local rates (12 erved vs. 5.3 expected). None of these were liver or biliary cancers. The number of deaths from hematologic neoplasms in females was higher than expected when compared with local rates (4 observed vs. 1.1 expected). This study is limited by several factors, particularly the small number of deaths that occurred by the cut-off period. The power of the study is insufficient to detect an elevated risk of site-specific cancer. In addition, the authors stated, after an examination of the individual cases, that interpretation of the increase in GI tract cancer in males was limited, as it appeared likely that some of these individuals had only limited PCB exposure. Confounding factors may have included possible contamination of the PCBs by dibenzofurans and exposure of some of the workers to trichloroethylene, alkylbenzene, and epoxy resins.

Two occurrences of ingestion of PCB-contaminated rice oil have been reported: the Yusho incident of 1968 in Japan and the Yu-Cheng incident of 1979 in Taiwan. Amano et al. (1984) completed a 16-year retrospective cohort mortality study of 581 male and 505 female victims of the Yusho incident. A consistently high risk of liver cancer in females over the entire 16 years was observed; liver cancer in males was also significantly increased. Several serious limitations are evident in this study. There was a lack of information regarding job histories or the influence of alcoholism or smoking. The information concerning the diagnosis of liver cancer was obtained from the victims' families, and it is not clear whether this information was independently verified by health professionals. For some of the cancers described, the latency period is shorter than would be expected. Furthermore, contaminated oils contained polychlorinated dibenzofurans and ychlorinated quinones as well as PCBs, and the study lacks data regarding exposure to the first two classes of compounds. There is strong evidence indicating that the health effects seen in Yusho victims were due to ingestion of polychlorinated dibenzofurans, rather than to PCBs themselves (reviewed in

EPA, 1988). The results of the Amano et al. study can, therefore, be considered as no more than suggestive of carcinogenicity of PCBs.

ANIMAL CARCINOGENICITY DATA

Sufficient. PCB mixtures assayed in the following studies were commercial preparations and may not be the same as mixtures of isomers found in the environment. Although animal feeding studies demonstrate the carcinogenicity of commercial PCB preparations, it is not known which of the PCB congeners in such preparations are responsible for these effects, or if decomposition products, contaminants or metabolites are involved in the toxic response. Early bioassays with rats (Kimura and Baba, 1973; Ito et al., 1974) were inadequate to assess carcinogenicity due to the small number of animals and short duration of exposure to PCB. A long-term bioassay of Aroclor 1260 reported by Kimbrough et al. (1975) produced hepatocellular carcinomas in female Sherman rats when 100 ppm was administered for 630 days to 200 animals. Hepatocellular carcinomas and neoplastic nodules were observed in 14 and 78%, respectively, of the dosed animals, compared with 0.58 and 0%, respectively, of the controls.

The NCI (1978) reported results for 24 male and 24 female Fischer 344 rats treated with Aroclor 1254 at 25, 50, or 100 ppm for 104 to 105 weeks. Although carcinomas of the gastrointestinal tract were observed among the treated animals only, the incidence was not statistically significantly elevated. An apparent dose-related incidence of hepatic nodular hyperplasia in both sexes as well as hepatocellular carcinomas among mid- to high-dose treated males was reported (4-12%, compared to 0% in controls).

Norback and Weltman (1985) fed 70 male and 70 female Sprague-Dawley rats a diet containing Aroclor 1260 in corn oil at 100 ppm for 16 months, followed by a 50 ppm diet for an additional 8 months, then a basal diet for 5 months. Control animals (63 rats/sex) received a diet containing corn oil for 18 months, then a basal diet alone for 5 months. Among animals that survived for at least 18 months, females exhibited a 91% incidence (43/47) of hepatocellular carcinoma. An additional 4% (2/47) had neoplastic nodules. In males corresponding incidences were 4% (2/46) for carcinoma and 11% (5/46) for neoplastic nodules. Concurrent liver morphology studies were carried out on tissue samples obtained by partial hepatectomies of three animals/group at eight time points. These studies showed the sequential progression of liver lesions to hepatocellular carcinomas.

Orally administered PCB resulted in increased incidences of hepatocellular carcinomas in two mouse strains. Ito et al. (1973) treated male dd mice (12/group) with Kanechlors 500, 400 and 300 each at dietary levels of 100, 250 or 500 ppm for 32 weeks. The group fed 500 ppm of Kanechlor 500 had a 41.7% incidence of hepatocellular carcinomas and a 58.3% incidence of nodular hyperplasia. Hepatocelluar carcinomas and nodular hyperplasia were not observed in mice fed 100 or 250 ppm of Kanechlor 500, nor among those fed Kanechlors 400 or 300 at any concentrations.

Schaeffer et al. (1984) fed male Wistar rats diets containing 100 ppm of the PCB mixtures Clophen A 30 (30% chlorine by weight) or Clophen A 60 (60% chlorine by weight) for 800 days. The PCB mixtures were reported to be free of furans. Clophen A 30 was administered to 152 rats, Clophen A 60 to 141 rats,

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

139 rats received a standard diet. Mortality and histologic lesions were reported for animals necropsied during each 100-day interval for all three groups. Of the animals that survived the 800-day treatment period, 1/53 rats (2%) in the control group, 3/87 (3%) in the Clophen A 30 group and 52/85 (61%) in the Clophen A 60 group had developed hepatocellular carcinoma. The incidence in the Clophen A 60 group was significantly elevated in comparison to the control group. Neoplastic nodules were reported in 2/53 control, 35/87 Clophen A 30, and 34/85 Clophen A 60-treated animals. The incidence of nodules was significantly increased in both treatment groups in comparison to the control group. Neoplastic liver nodules and hepatocellular carcinomas appeared earlier and at higher incidence in the Clophen A 60 group relative to the Clophen A 30 group. The authors interpreted the results as indicative of a carcinogenic effect related to the degree of chlorination of the PCB mixture. The authors also suggested that these findings support those of others, including Ito et al. (1973) and Kimbrough et al. (1975), in which hepatocellular carcinomas were produced by more highly chlorinated mixtures.

Kimbrough and Linder (1974) dosed groups of 50 male BALB/cJ mice (a strain with a low spontaneous incidence of hepatoma) with Aroclor 1254 at 300 ppm in the diet for 11 months or 6 months, followed by a 5-month recovery period. Two groups of 50 mice were fed a control diet for 11 months. The incidence of hepatomas in survivors fed Aroclor 1254 for 11 months was 10/22. One hepatoma was observed in the 24 survivors fed Aroclor 1254 for 6 months.

. ORTING DATA FOR CARCINOGENICITY

Most genotoxicity assays of PCBs have been negative. The majority of microbial assays of PCB mixtures and various congeners showed no evidence of mutagenic effects (Schoeny et al., 1979; Schoeny, 1982; Wyndham et al., 1976). Of various tests on the clastogenic effect of PCBs (Heddle and Bruce, 1977; Green et al., 1975), only Peakall et al. (1972) reported results indicative of a possible clastogenic action by PCBs in dove embryos.

Chlorinated dibenzofurans (CDFs), known contaminants of PCBs, and chlorinated dibenzodioxins (CDDs) are structurally related to and produce certain biologic effects similar to those of PCB congeners. While the CDDs are known to be carcinogenic, the carcinogenicity of CDFs is still under evaluation.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Slope Factor: 7.7E+0 per mg/(kg/day)
Unit Risk: 2.2E-4 per ug/liter
Extrapolation Method: Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E-1 ug/liter
-5 (1 in 100,000)	5E-2 ug/liter
-6 (1 in 1,000,000)	5E-3 ug/liter

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type: trabecular carcinoma/adenocarcinoma, neoplastic nodule
Test Animals: rat/Sprague-Dawley, female
Route: diet

Administered Dose (mg/kg)/day (TWA)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	1/49
3.45	0.59	45/47

ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Human equivalent dosage assumes a TWA daily dose of 3.45 mg/kg/day. This reflects the dosing schedule of 5 mg/kg/day (assuming the rat consumes an amount equal to 5% of its bw/day) for the first 16 months, 2.5 mg/kg/day for the next 8 months, and no dose for the last 5 months.

A slope factor of 3.9/mg/kg/day was based on data from the Kimbrough et al. (1975) study of female Sherman rats fed Aroclor 1260. The estimate based on the data of Norback and Weltman (1985) is preferred because Sprague-Dawley rats are known to have low incidence of spontaneous hepatocellular neoplasms. Moreover, the latter study spanned the natural life of the animal, and concurrent morphologic liver studies showed the sequential progression of liv lesions to hepatocellular carcinomas.

Although it is known that PCB congeners vary greatly as to their potency in producing biological effects, for purposes of this carcinogenicity assessment Aroclor 1260 is intended to be representative of all PCB mixtures. There is some evidence that mixtures containing more highly chlorinated biphenyls are more potent inducers of hepatocellular carcinoma in rats than mixtures containing less chlorine by weight (reviewed in Kimbrough, 1987 and Schaeffer et al., 1984).

The unit risk should not be used if the water concentration exceeds 50 ug/L, since above this concentration the slope factor may differ from that stated.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The Norback and Weltman study used an adequate number of animals, observed for their normal lifespan. Only one non-zero test dose was used. A second risk estimate was also calculated based on the numbers of malignant tumors alone, as called for in the EPA's guidelines for carcinogen risk assessment. The slope factor thus derived is 5.7/mg/kg/day, which is 26% less than that derived using combined malignant tumors and neoplastic nodules. This risk estimate is supported by one based on data of Kimbrough et al. (1975).

PCB mixtures in drinking water may not be the same as the mixtures introduced or used for testing carcinogenicity in animals.

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

— QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE —

No Data Available

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1988. Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

The 1988 Drinking Water Criteria Document for PCBs has received OHEA review.

Agency Work Group Review: 04/22/87

Verification Date: 04/22/87

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REVISION HISTORY

01/90 Ca Data: Text edited

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

ubstance Name: p,p'-Dichlorodiphenyl dichloroethane (DDD)
ASRN: 72-54-8

he Carcinogenicity Assessment Section provides information on three aspects of he carcinogenic risk assessment for the agent in question; the U.S. EPA lassification, and quantitative estimates of risk from oral exposure and from nhalation exposure. The classification reflects a weight-of-evidence judgment f the likelihood that the agent is a human carcinogen. The quantitative risk stimates are presented in three ways. The slope factor is the result of pplication of a low-dose extrapolation procedure and is presented as the risk er mg/kg/day. The unit risk is the quantitative estimate in terms of either isk per ug/L drinking water or risk per ug/cu.m air breathed. The third form n which risk is presented is a drinking water or air concentration providing ancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The Carcinogen ssessment Background Document provides details on the rationale and methods sed to derive the carcinogenicity values found in IRIS. Users are referred to he Oral RfD and Inhalation RfC Sections for information on long-term toxic ffects other than carcinogenicity.

EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

EIGHT-OF-EVIDENCE CLASSIFICATION

lassification: B2; probable human carcinogen

ASIS

ased on an increased incidence of lung tumors in male and female mice, liver mors in male mice and thyroid tumors in male rats. DDD is structurally nilar to, and is a known metabolite of DDT, a probable human carcinogen.

AN CARCINOGENICITY DATA

ne. Human epidemiological data are not available for DDD. Evidence for the rcinogenicity in humans of DDT, a structural analog, is based on autopsy udies relating tissue levels of DDT to cancer incidence. These studies have elded conflicting results. Three studies reported that tissue levels of DDT d DDE were higher in cancer victims than in those dying of other diseases asarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In her studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 65; Hoffman et al., 1967). Studies of occupationally exposed workers and lunteers have been of insufficient duration to determine the carcinogenicity DDT to humans.

IMAL CARCINOGENICITY DATA

fficient. Tomatis et al. (1974) fed DDD for 130 weeks at 250 ppm (TWA) to 60 -1 mice/sex. A statistically significant increase in incidence of lung mors was seen in both sexes compared with controls. In males, a atistically significant increase in incidence of liver tumors was also seen.

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

(1978) fed DDD at 411 and 822 ppm (TWA) to 50 B6C3F1 mice/sex/dose for 78 weeks. Actual doses were 350 or 630 ppm for 5 weeks, 375 or 750 ppm for 11 weeks, and 425 or 850 ppm for the next 62 weeks. After an additional 15 weeks, an increased incidence of hepatocellular carcinomas was seen in both sexes by comparison to controls, but the increase was not statistically significant.

NCI (1978) also fed DDD at 1647 and 3294 ppm TWA for males and 850 and 1700 ppm TWA for females for 78 weeks to 50 Osborne-Mendel rats/sex/dose. Males were fed 1400 or 2800 ppm for 23 weeks followed by 1750 or 3500 ppm for 55 weeks. Females were fed 850 or 1700 ppm for the entire 78 weeks. After an additional 35 weeks, an increased incidence of thyroid tumors (follicular cell adenomas and carcinomas) was observed in males. Due to a wide variation in incidence of these tumors in the control groups for DDD, DDE and DDT, the increased incidence was not statistically significant by comparison to concurrent controls. Although tumor incidence did not appear to be dose-related, the increase was significant at the low dose by comparison to historical controls. Thus, the pathologists' judgment and statistical results suggest a possible carcinogenic effect of DDD in male rats. NCI concluded that a definitive interpretation of the data was not possible.

SUPPORTING DATA FOR CARCINOGENICITY

DDD is structurally similar to, and is a metabolite of, DDT, a probable human carcinogen, in rats (Peterson and Robinson, 1964), mice (Gingell and Wallcave,), and humans (Morgan and Roan, 1977).

Positive effects were found with DDD in mammalian cytogenetic assays and a host-mediated assay (ICPEMC, 1984).

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Slope Factor: 2.4E-1 per mg/(kg/day)
Unit Risk: 6.9E-6 per ug/liter
Extrapolation Method: Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/liter
E-5 (1 in 100,000)	1E+0 ug/liter
E-6 (1 in 1,000,000)	1E-1 ug/liter

DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type: liver
Test Animals: mouse/CF-1, males
Route: diet

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	33/98
250	245	31/59

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

DDD used in the Tomatis study was 99% pure p,p'-isomer. In the NCI bioassay, technical grade DDD was used, in which 60% of the material consisted of the p,p'-isomer. The composition of the remaining 40% was unspecified, but it was stated that analysis by gas chromatography revealed at least 19 impurities.

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was tested. The slope factor was calculated using tumor incidence data from only one dose. The slope factor was similar to, and within a factor of 2, of the slope factors for this same site of three other structurally similar compounds: DDT, 3.4E-1/mg/kg/day; DDE, 3.4E-1/mg/kg/day; and dicofol, 4.4E-1/mg/kg/day.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

No Data Available

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1980. Hazard Assessment Report on DDT, DDD, DDE Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. The Carcinogenic Assessment Group's Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, carcinogen Assessment Group, Washington, DC, for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC. (Internal Report) EPA-600/X-85-097.

The 1985 Carcinogen Assessment Group's report has received Agency review.

The 1980 Hazard Assessment Report has received peer review.

Agency Work Group Review: 06/03/87, 06/24/87

Verification Date: 06/24/87

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CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name: p,p'-Dichlorodiphenyldichloroethylene (DDE)
CASRN: 72-55-9

The Carcinogenicity Assessment Section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The Carcinogen Assessment Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to the Oral RfD and Inhalation RfC Sections for information on long-term toxic effects other than carcinogenicity.

EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification: B2; probable human carcinogen

BASIS

increased incidence of liver tumors including carcinomas in two strains of mice and in hamsters and of thyroid tumors in female rats by diet.

HUMAN CARCINOGENICITY DATA

Human epidemiological data are not available for DDE. Evidence for the carcinogenicity in humans of DDT, a structural analog, is based on autopsy studies relating tissue levels of DDT to cancer incidence. These studies have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases (Casarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In other studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 1965; Hoffman et al., 1967). Studies of volunteers and workers occupationally exposed to DDT have been of insufficient duration to determine the carcinogenicity of DDT to humans.

ANIMAL CARCINOGENICITY DATA

Sufficient. NCI (1978) administered DDE in feed at TWA doses of 148 and 261 ppm to 50 B6C3F1 mice/sex/dose for 78 weeks. After an additional 15 weeks, a dose-dependent and statistically significant increase in incidence of hepatocellular carcinomas was observed in males and females in comparison with controls. Increased weight loss and mortality was observed in females.

atis et al. (1974) administered 250 ppm DDE in feed for lifetime (130 weeks) to 60 CF-1 mice/sex. A statistically significant increase in incidence of hepatomas was observed in both males and females in comparison with controls. In females, 98% of the 55 surviving exposed animals developed hepatomas, compared to 1% of the surviving controls.

Rossi et al. (1983) administered DDE in feed for 128 weeks to 40-46 Syrian Golden hamsters/sex/dose at doses of 500 and 1000 ppm. After 76 weeks, a statistically significant increase in incidence of neoplastic nodules of the liver were observed in both sexes in comparison with vehicle-treated controls.

NCI (1978) also fed DDE at TWA doses of 437 and 839 ppm for males and 242 and 462 ppm for females for 78 weeks to 50 Osborne-Mendel rats/sex/ dose, with an additional 35 week observation period. A dose-dependent trend in incidence of thyroid tumors was observed in females which was statistically significant by the Cochran Armitage trend test after adjustment for survival. The Fischer Exact test, however, was not statistically significant. Overall, the results of the bioassay were not considered by NCI to provide convincing evidence for carcinogenicity.

SUPPORTING DATA FOR CARCINOGENICITY

DDE was mutagenic in mouse lymphoma (L5178Y) cells and chinese hamster (V79) cells, but not in Salmonella (ICPEMC, 1984). DDE is structurally similar to a metabolite of DDT (Peterson and Robinson, 1964; Gingell and Wallcave, 1976; Morgan and Roan, 1977) which is a probable human carcinogen.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Slope Factor: 3.4E-1 per mg/(kg/day)
Unit Risk: 9.7E-6 per ug/liter
Extrapolation Method: Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/liter
E-5 (1 in 100,000)	1E+0 ug/liter
E-6 (1 in 1,000,000)	1E-1 ug/liter

DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type: hepatocellular carcinomas, hepatomas
Test Animals: mouse/B6C3F1; mouse/CF-1; hamsters/Syrian Golden
Route: diet

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence female	male	Reference
e/B6C3F1; hepatocellular carcinomas				
0	0.0	0/19	0/19	NCI, 1978
148	0.90	19/47	7/41	
261	1.584	34/48	17/4	

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Mouse/CF-1; hepatomas				
0	0	1/90	33/98	Tomatis et
250	2.45	54/55	39/53	al., 1974
Hamsters/Syrian Golden; neoplastic nodules (hepatomas)				
0	0	0/31	0/42	Rossi et
500	4.79	7/30	4/39	al., 1983
1000	9.57	8/39	6/39	

ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

NCI (1978) used DDE of about 95% purity, while that used by Tomatis et al. (1974) and Rossi et al. (1983) was 99% pure. In the hamster study, Rossi et al. described the observed lesions as neoplastic liver nodules or hepatocellular tumors, using these terms interchangeably. The oral quantitative estimate is a geometric mean of six slope factors computed from incidence data by sex from the studies cited previously (Animal Data).

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was observed. The geometric mean obtained using the slope factors from the mouse studies alone is 7.8E-1/mg/kg/day. This is within a factor of 2 of that derived from the mouse and hamster studies combined. In addition, the slope factor for DDE was within a factor of 2 of the slope factors for liver tumors for three structurally similar compounds: DDT, 3.4E-1/mg/kg/day; DDD, 2.4E-1/mg/kg/day; and Dicofol, 4.4E-1/mg/kg/day.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

No Data Available

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1980. Hazard Assessment Report on DDT, DDD, DDE. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. The Carcinogen Assessment Group's Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC.

The 1985 Carcinogen Assessment Group's report has received Agency review. The 1980 Hazard Assessment Report has received peer review.

Agency Work Group Review: 06/24/87

Verification Date: 06/24/87

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CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name: p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN: 50-29-3

The Carcinogenicity Assessment Section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The Carcinogen Assessment Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to the Oral RfD and Inhalation RfC Sections for information on long-term toxic effects other than carcinogenicity.

EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification: B2; probable human carcinogen

BASIS

Observation of tumors (generally of the liver) in seven studies in various mouse strains and three studies in rats. DDT is structurally similar to other probable carcinogens, such as DDD and DDE.

HUMAN CARCINOGENICITY DATA

Inadequate. The existing epidemiological data are inadequate. Autopsy studies relating tissue levels of DDT to cancer incidence have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases (Casarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In other studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 1965; Hoffman et al., 1967). Studies of occupationally exposed workers and volunteers have been of insufficient duration to be useful in assessment of the carcinogenicity of DDT to humans.

ANIMAL CARCINOGENICITY DATA

Sufficient. Twenty-five animal carcinogenicity assays have been reviewed fo DDT. Nine feeding studies, including two multigenerational studies, have been conducted in the following mouse strains: BALB/C, CF-1, A strain, Swiss/Bombay and (C57B1)x(C3HxAkR). Only one of these studies, conducted for 78 weeks, showed no indication of DDT tumorigenicity (NCI, 1978). Both hepatocellular adenomas and carcinomas were observed in six mouse liver tumor studies (Walker

al., 1973; Thorpe and Walker, 1973; Kashyap et al., 1977; Innes et al., 1969; Terracini et al., 1973; Turusov et al., 1973). Both benign and malignant lung tumors were observed in two studies wherein mice were exposed both in utero and throughout their lifetime (Shabad et al., 1973; Tarjan and Kemeny, 1969). Doses producing increased tumor incidence ranged from 0.15-37.5 mg/kg/day.

Three studies using Wistar, MRC Porton and Osborne-Mendel rats and doses from 25-40 mg/kg/day produced increased incidence of benign liver tumors (Rossi et al., 1977; Cabral et al., 1982; Fitzhugh and Nelson, 1946). Another study wherein Osborne-Mendel rats were exposed in this dietary dose range for 78 weeks was negative (NCI, 1978) as were three additional assays in which lower doses were given.

Tests of DDT in hamsters have not resulted in increased tumor incidence. Unlike mice and humans, hamsters accumulate DDT in tissue but do not metabolize it to DDD or DDE. Studies of DDT in dogs (Lehman, 1951, 1965) and monkeys (Adamson and Sieber, 1979, 1983) have not shown a carcinogenic effect. However, the length of these studies (approximately 30% of the animals' lifetimes) was insufficient to assess the carcinogenicity of DDT. DDT has been shown to produce hepatomas in trout (Halver, 1967).

SUPPORTING DATA FOR CARCINOGENICITY

DDT has been shown to act as a liver tumor promoter in rats initiated with 2 -etylaminofluorene, 2-acetamidophenanthrene or trans-4-acetylaminostilbene (aino et al., 1975; Scribner and Mottet, 1981; Hilpert et al., 1983).

DDT has produced both negative and positive responses in tests for genotoxicity. Positive responses have been noted in V79 mutation assays, for chromosome aberrations in cultured human lymphocytes, and for sister chromatid exchanges in V79 and CHO cells (Bradley et al., 1981; Rabello et al., 1975; Preston et al., 1981; Ray-Chaudhuri et al., 1982). In one study, DDT was reported to interact directly with DNA; this result was not confirmed in the absence of a metabolizing system (Kubinski et al., 1981; Griffin and Hill, 1978).

DDT is structurally related to the following chemicals which produce liver tumors in mice: DDE, DDD, dicofol and chlorobenzilate.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Slope Factor: 3.4E-1 per mg/(kg/day)
Unit Risk: 9.7E-6 per ug/liter
Extrapolation Method: Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/liter
E-5 (1 in 100,000)	1E+0 ug/liter
6 (1 in 1,000,000)	1E-1 ug/liter

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type: Liver, benign and malignant (see table)
Test Animals: mouse and rat (see table)
Route: diet

Species/Strain Tumor Type	Slope Factor Male	Slope Factor Female	Reference
Mouse/CF-1, Benign	0.80	0.42	Turusov et al., 1973
Mouse/BALB/C, Benign	0.082		Terracini et al., 1973
Mouse/CF-1, Benign, Malignant	0.52	0.81	Thorpe and Walker, 1973
Mouse/CF-1, Benign	1.04	0.49	Tomatis and Turusov, 1975
Rat/MRC Porton		0.084	Cabral et al., 1982
Rat/Wistar, Benign	0.16	0.27	Rossi et al., 1977

ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The estimate of the slope factor did not increase in the multigeneration feeding studies (Terracini et al., 1973; Turusov et al., 1973) but remained the same from generation to generation. A geometric mean of the above slope factors was used for the overall slope factor of 3.4E-1. This was done in order to avoid excluding relevant data (note that the appropriateness of this procedure is currently under study by U.S. EPA). All tumors were of the liver; there were no metastases. A few malignancies were observed in the Turusov study; possible neoplasms were indicated in the Terracini and Tomatis studies. The Turusov study was carried out over six generations, the Terracini assay for two. The slope factor derived from data of Tarjan and Kemeny (1969) was not included in the calculation of the geometric mean because the tumors developed at different sites than in any other studies. In addition, there was a problem in this study with possible DDT contamination of the feed.

DDT is known to be absorbed by humans in direct proportion to dietary exposure; t(1/2) for clearance is 10-20 years.

The unit risk should not be used if the water concentraion exceeds 1E+3 ug/L, since above this concentration the unit risk may not be appropriate.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Ten slope factors derived from six studies were within a 13-fold range. The slope factor derived from the mouse data alone was 4.8E-1 while that derived from the rat data alone was 1.5E-1. There was no apparent difference in slope factor as a function of sex of the animals. The geometric mean of the slope factors from the mouse and rat data combined was identical for the same tumor site as that for DDE [3.4E-1 per (mg/kg)/day], a structural analog.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Unit Risk: 9.7E-5 per (ug/cu.m)
Extrapolation Method: Linear multistage procedure, extra risk

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+0 per (ug/cu.m)
E-5 (1 in 100,000)	1E-1 per (ug/cu.m)
E-6 (1 in 1,000,000)	1E-2 per (ug/cu.m)

DOSE-RESPONSE DATA (CARCINOGENICITY, INHALATION EXPOSURE)

The inhalation risk estimates were calculated from the data given in the oral exposure data table.

ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk should not be used if the air concentration exceeds 1E+2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

See oral quantitative estimate.

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1985. The Carcinogenic Assessment Groups Calculation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Hazard Evaluation Division, Office of Toxic Substances, Washington, DC.

The U.S. EPA risk assessment document on DDT is an internal report and has not received external review.

Agency Work Group Review: 10/29/86, 11/12/86, 06/24/87

Verification Date: 06/24/87

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REVISION HISTORY

01/91 Ca Data:	Text edited
01/91 Ca In Summ:	Inhalation slope factor removed (global change)
05/91 Ca Animal:	Change Lehman, 1952 to '1951'

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

stance Name: Dieldrin
SRN: 60-57-1

The Carcinogenicity Assessment Section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The Carcinogen Assessment Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to the Oral RfD and Inhalation RfC Sections for information on long-term toxic effects other than carcinogenicity.

EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

WEIGHT-OF-EVIDENCE CLASSIFICATION

sification: B2; probable human carcinogen

BASIS

Dieldrin is carcinogenic in seven strains of mice when administered orally. Dieldrin is structurally related to compounds (aldrin, chlordane, heptachlor, heptachlor epoxide, and chlorendic acid) which produce tumors in rodents.

HUMAN CARCINOGENICITY DATA

Inadequate. Two studies of workers exposed to aldrin and to dieldrin reported no increased incidence of cancer. Both studies were limited in their ability to detect an excess of cancer deaths. Van Raalte (1977) observed two cases of cancer (gastric and lymphosarcoma) among 166 pesticide manufacturing workers exposed 4-19 years and followed from 15-20 years. Exposure was not quantified, and workers were also exposed to other organochlorine pesticides (endrin and telodrin). The number of workers studied was small, the mean age of the cohort (47.7 years) was young, the number of expected deaths was not calculated, and the duration of exposure and of latency was relatively short.

In a retrospective mortality study, Ditraglia et al. (1981) reported no statistically significant excess in deaths from cancer among 1155 organochlorine pesticide manufacturing workers [31 observed vs. 37.8 expected, S dardized Mortality Ratio (SMR) = 82]. Workers were employed for 6 months c. ore and followed 13 years or more (24,939 person-years). Workers with no exposure (for example, office workers) were included in the cohort. Vital status was not known for 112 or 10% of the workers, and these workers were assumed to be alive; therefore additional deaths may have occurred but were not observed. Exposure was not quantified and workers were also exposed to other

chemicals and pesticides (including endrin). Increased incidences of deaths from cancer were seen at several specific sites: esophagus (2 deaths observed, SMR = 235); rectum (3, SMR = 242); liver (2, SMR = 225); and lymphatic and hematopoietic system (6, SMR = 147), but these site-specific incidences were not statistically significantly increased.

ANIMAL CARCINOGENICITY DATA

Sufficient. Dieldrin has been shown to be carcinogenic in various strains of mice of both sexes. At different dose levels the effects range from benign liver tumors, to hepatocarcinomas with transplantation confirmation, to pulmonary metastases.

The Food and Drug Administration (FDA) conducted a long-term carcinogenesis bioassay for dieldrin (Davis and Fitzhugh, 1962). Ten ppm dieldrin was administered orally to 218 male and female C3HeB/Fe mice for 2 years. The study was compromised by the poor survival rate, lack of detailed pathology, loss of a large percentage of the animals to the study, and failure to treat the data for males and females separately. A statistically significant increase in incidence of hepatomas was observed in the treated groups versus the control groups in both males and females. In FDA follow-up study, Davis (1965) examined 100 male and 100 female C3H mice which had been orally administered 10 ppm dieldrin. The same limitations as the previous study were reported. The incidence of benign hepatomas and hepatic carcinomas was significantly increased in the dieldrin group. A reevaluation of the histological material of both studies was done by Reuber in 1974 (Epstein, 1975a,b; 1976). He concluded that the hepatomas were malignant and that dieldrin was hepatocarcinogenic for male and female C3HeB/Fe and C3H mice.

Walker et al. (1972) conducted several studies of dieldrin in CF1 mice of both sexes. Dieldrin was administered orally at concentrations of 0, 0.1, 1.0, and 10 ppm. Treatment groups varied from 87 to 288 animals of each sex. Surviving animals were sacrificed during weeks 132-140. Incidence of tumors was related to the number of dose levels and the dose administered. Effects were detected at the lowest dieldrin level tested (0.1 ppm) in both male and female mice. Dieldrin also produced significant increases (<0.05) in the incidence of pulmonary adenomas, pulmonary carcinomas, lymphoid tumors, and "other" tumors in female mice.

Diets containing 10 ppm dieldrin were fed to groups of 30 CF1 mice of both sexes for 110 weeks (Thorpe and Walker, 1973). The control group consisted of 45 mice of both sexes. A statistically significant increase ($p<0.01$) in incidence of liver tumors was found in both sexes of treated animals relative to controls. The liver tumors appeared much earlier in treated animals than controls.

Technical-grade dieldrin (>96%) was fed to B6C3F1 mice (50/sex/dose) at TWA doses of 0, 2.5, or 5 ppm for 80 weeks followed by an observation period of 10 to 13 weeks (NCI, 1978a). Matched control groups consisted of 20 untreated males and 10 untreated females. No significant difference in survival was noted. A significant dose-related increase in hepatocellular carcinoma was found in male mice when compared with pooled controls.

Tennekes et al. (1981) fed groups of 19 to 82 male CF1 mice control or

eldrin-supplemented (10 ppm) diets or control diets for 110 weeks. Dieldrin oduced a statistically significant increased incidence of hepatocellular carcinomas in the treated group.

Dieldrin (>99%) was continuously fed in the diet for 85 weeks to 50 C3H/He, 62 B6C3F1, and 71 C57B1/6J male mice (Meierhenry et al., 1983). Controls were 50 to 76 males of each strain. Dieldrin produced a significant increase in the incidence of hepatocellular carcinomas compared with controls in all three strains.

Seven studies with four strains of rats fed 0.1 to 285 ppm dieldrin varying in duration of exposure from 80 weeks to 31 months did not produce positive results for carcinogenicity (Treon and Cleveland, 1955; Fitzhugh et al., 1964; Song and Harville, 1964; Walker et al., 1969; Deichmann et al., 1970; NCI, 1978a,b). Three of these studies used Osborne-Mendel rats, two studies used Carworth rats, and one each used Fischer 344 and Holtzman strains. Only three of the seven studies are considered adequate in design and conduct. The others used too few animals, had unacceptably high levels of mortality, were too short in duration, and/or had inadequate pathology examination or reporting.

SUPPORTING DATA FOR CARCINOGENICITY

Dieldrin causes chromosomal aberrations in mouse cells (Markaryan, 1966; Majumdar et al., 1976) and in human lymphoblastoid cells (Trepanier et al., 7), forward mutation in Chinese hamster V79 cells (Ahmed et al., 1977), and cheduled DNA synthesis in rat (Probst et al., 1981) and human cells (Rocchi et al., 1980). Dieldrin did not produce responses in 13 other mutagenicity tests. Negative responses were given in assays for gene conversion in S. cerevisiae, back-mutation in S. marcesans, forward mutation (Gal Rz2 in E. coli), and forward mutation to streptomycin resistance in E. coli (Fahrig, 1974). Negative responses were produced in reverse mutation assays with six strains of S. typhimurium with or without metabolic activation (Bidwell et al., 1975; Marshall et al., 1976; Shirasu et al., 1976; Wade et al., 1979; Haworth et al., 1983). Majumdar et al. (1977), however, reported that dieldrin was mutagenic for S. typhimurium with and without metabolic activation.

Five compounds structurally related to dieldrin - aldrin, chlordane, heptachlor, heptachlor epoxide, and chlorondic acid - have induced malignant liver tumors in mice. Chlorendic acid has also induced liver tumors in rats.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Slope Factor:	1.6E+1 per mg/(kg/day)
Unit Risk:	4.6E-4 per ug/liter
Extrapolation Method:	Linearized multistage procedure, extra risk

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-1 ug/liter
E-5 (1 in 100,000)	2E-2 ug/liter
E-6 (1 in 1,000,000)	2E-3 ug/liter

DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type: liver carcinoma
Test Animals: mouse
Route: diet

Sex/Strain	Slope Factor	Reference
Male, C3H	22	Davis (1965), reevaluated by Reuber, 1974 (cited in Epstein, 1975a)
Female, C3H	25	Davis (1965), reevaluated by Reuber, 1974 (cited in Epstein, 1975a)
Male, CF1	25	Walker et al. (1972)
Female, CF1	28	Walker et al. (1972)
Male, CF1	15	Walker et al. (1972)
Female, CF1	7.1	Walker et al. (1972)
Male, CF1	55	Thorpe and Walker (1973)
Female, CF1	26	Thorpe and Walker (1973)
Male, B6C3F1	9.8	NCI (1978a,b)
Male, CF1	18	Tennekes et al. (1981)
Male, C57B1/6J	7.4	Meierhenry et al. (1983)
Male, C3H/He	8.5	Meierhenry et al. (1983)
Male, B6C3F1	11	Meierhenry et al. (1983)

ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The slope factor is the geometric mean of 13 slope factors calculated from liver carcinoma data in both sexes of several strains of mice. Inspection of the data indicated no strain or sex specificity of carcinogenic response.

The unit risk should not be used if the water concentration exceeds 20 ug/L,

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

:e above this concentration the unit risk may not be appropriate.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The individual slope factors calculated from 13 independent data sets range within a factor of 8.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Unit Risk: 4.6E-3 per (ug/cu.m)
Extrapolation Method: Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 per (ug/cu.m)
E-5 (1 in 100,000)	2E-3 per (ug/cu.m)
E-6 (1 in 1,000,000)	2E-4 per (ug/cu.m)

DOSE-RESPONSE DATA (CARCINOGENICITY, INHALATION EXPOSURE)

The inhalation risk estimates were calculated from the data given in the oral exposure data table.

ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk should not be used if air concentrations exceed 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

See oral quantitative estimate.

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1986. Carcinogenicity Assessment of Aldrin and Dieldrin. Prepared by Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, DC for Hazard Evaluation Division, Office of Pesticide Programs, Office of Pesticides and Toxic Substances. OHEA-C-205.

Agency Work Group Review: 03/05/87

Verification Date: 03/05/87

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REVISION HISTORY

03/90 Ca Animal:	Reuber citation year and Deichman spelling corrected
03/90 Ca Human:	Ditraglia citation clarified
03/90 Ca Or Data:	Reuber citation year corrected
03/90 Ca Support:	Shirasu citation year corrected
04/90 Ca Refs:	Treon and Cleveland, 1955 citation corrected
09/90 Ca Data:	Text edited
01/91 Ca Data:	Text edited
01/91 Ca In Summ:	Inhalation slope factor removed (global change)

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN: 50-29-3

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 0.05 mg/kg-day [Study 1 NOAEL(adj)]
UF: 100 MF: 1 RfD: 5E-4 mg/kg-day Confidence: Medium

Crit Effect: (1) Liver lesions

ported	NOAEL (Study 1)	LOAEL (Study 1)
	1 ppm diet	5 ppm
ADJ	0.05 mg/kg-day	0.25 mg/kg-day
Study Type	27-Week Rat Feeding Study	27-Week Rat Feeding Study
Reference	Laug et al., 1950	Laug et al., 1950

1) Laug et al., 1950
27-Week Rat Feeding Study

Critical Effect: Liver lesions

Defined Dose Levels:
NOAEL= 1 ppm diet
NOAEL(ADJ)= 0.05 mg/kg-day
LOAEL= 5 ppm
LOAEL(ADJ)= 0.25 mg/kg-day

Conversion Factors: Food consumption = 5% bw/day

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

, E.P., A.A. Nelson, O.G. Fitzhugh and F.M. Kunze. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1-50 ppm DDT. J. Pharmacol. Exp. Therap. 98: 268-273.

Weanling rats (25/sex/group) were fed commercial DDT (65% p,p' isomer and 19%

O,P isomer) at levels of 0, 1, 5, 10 or 50 ppm for 15-27 weeks. The diet was prepared by mixing appropriate amounts of DDT in corn oil solution with powdered chow. No interference with growth was noted at any level. Females stored more DDT in peripheral fat than did males, but pathologic changes were seen to a greater degree in males. Increasing hepatocellular hypertrophy, especially centrilobularly, increased cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules (based on H and E paraffin sections) were observed at dose levels of 5 ppm and above. The effect was minimal at 5 ppm (LOAEL) and more pronounced at higher doses. No effects were reported at 1 ppm, the NOEL level used as the basis for the RfD calculation. The authors believe the effect seen at 5 ppm "represents the smallest detectable morphologic effect, based on extensive observations of the rat liver as affected by a variety of chemicals."

DDT fed to rats for 2 years (Fitzhugh, 1948) caused liver lesions at all dose levels (10-800 ppm of diet). A LOAEL of 0.5 mg/kg bw/day was established. Application of a factor of 10 each for uncertainty of estimating a NOEL from a LOAEL, as well as for interspecies conversion and protection of sensitive human subpopulations (1000 total) results in the same RfD level as that calculated from the critical study. DDT-induced liver effects were observed in mice, hamsters and dogs as well.

The Laug et al. (1950) study was chosen for the RfD calculation because: 1) male rats appear to be the most sensitive animals to DDT exposure; 2) the study was of sufficient length to observe toxic effects; and 3) several doses were administered in the diet over the range of the dose-response curve. This stu also established a LOAEL and a NOEL, with the LOAEL (0.25 mg/kg/day) being the lowest of any observed for this compound.

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

A factor of 10 each was applied for the uncertainty of interspecies conversion and to protect sensitive human subpopulations. An uncertainty factor for subchronic to chronic conversion was not included because of the corroborating chronic study in the data base.

ADDITIONAL COMMENTS / STUDIES

In one 3-generation rat reproduction study (Treon and Cleveland, 1955), offspring mortality increased at all dose levels, the lowest of which corresponds to about 0.2 mg/kg bw/day. Three other reproduction studies (rat and mouse) show no reproductive effects at much higher dose levels.

CONFIDENCE IN THE RfD

Study: Medium Data Base: Medium RfD: Medium

The principal study appears to be adequate, but of shorter duration than that desired; therefore, confidence in the study can be considered medium to low. The data base is only moderately supportive of both the critical effect and th magnitude, and lacks a clear NOEL for reproductive effects; therefore, confidence in the data base can also be considered medium to low. Medium to low confidence in the RfD follows.

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

EPA DOCUMENTATION AND REVIEW

Source Document: This assessment is not presented in any existing U.S. EPA document.

Agency Work Group Review: 12/18/85

Verification Date: 12/18/85

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REVISION HISTORY

01/92 RfD Contact: Secondary contact changed

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Dieldrin
CASRN: 60-57-1

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 0.005 mg/kg-day [Study 1 NOAEL(adj)]
UF: 100 MF: 1 RfD: 5E-5 mg/kg-day Confidence: Medium

Crit Effect: (1) Liver lesions

	NOAEL (Study 1)	LOAEL (Study 1)
Reported	0.1 ppm	1.0 ppm
ADJ	0.005 mg/kg-day	0.05 mg/kg-day
Study Type	2-Year Rat Feeding Study	2-Year Rat Feeding Study
Reference	Walker et al., 1969	Walker et al., 1969

1) Walker et al., 1969
2-Year Rat Feeding Study

Critical Effect: Liver lesions

Defined Dose Levels:
NOAEL= 0.1 ppm
NOAEL(ADJ)= 0.005 mg/kg-day
LOAEL= 1.0 ppm
LOAEL(ADJ)= 0.05 mg/kg-day

Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

Walker, A.I.T., D.E. Stevenson, J. Robinson, R. Thorpe and M. Roberts. 1969. The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. Toxicol. Appl. Pharmacol. 15: 345-373.

Walker et al. (1969) administered dieldrin (recrystallized 99% active

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

edient) to Carworth Farm "E" rats (25/sex/dose; controls 45/sex) for 2 s at dietary concentrations of 0, 0.1, 1.0, or 10.0 ppm. Based on intake assumptions presented by the authors, these dietary levels are approximately equal to 0, 0.005, 0.05 and 0.5 mg/kg/day. Body weight, food intake, and general health remained unaffected throughout the 2-year period, although at 10.0 ppm (0.5 mg/kg/day) all animals became irritable and exhibited tremors and occasional convulsions. No effects were seen in various hematological and clinical chemistry parameters. At the end of 2 years, females fed 1.0 and 10.0 ppm (0.05 and 0.5 mg/kg/day) had increased liver weights and liver-to-body weight ratios ($p<0.05$). Histopathological examinations revealed liver parenchymal cell changes including focal proliferation and focal hyperplasia. These hepatic lesions were considered to be characteristic of exposure to an organochlorine insecticide. The LOAEL was identified as 1.0 ppm (0.005 mg/kg/day) and the NOAEL as 0.1 ppm (0.005 mg/kg/day).

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

The UF of 100 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A) and uncertainty in the threshold for sensitive humans (10H).

ADDITIONAL COMMENTS / STUDIES

D considered for establishing the RfD:

1) 2-Year Feeding - rat: Principal study - see previous description

2) 2-Year Feeding (oncogenic) - dog: Systemic NOEL=0.005 mg/kg/day; LEL= 0.05 mg/kg/day (increased liver weight and liver/body weight ratios, increased plasma alkaline phosphatase, and decreased serum protein concentration) (Walker et al., 1969)

3) 2-Year Feeding - rat: Systemic LEL=0.5 ppm (approximately 0.025 mg/kg/day), (liver enlargement with histopathology); (Fitzhugh et al., 1964)

4) 2-Year Feeding (oncogenic) - mouse: Systemic LEL=0.1 ppm (0.015 mg/kg/day), (liver enlargement with histopathology); (Walker et al., 1972)

5) 25-Month Feeding - dog: Systemic NOEL=0.2 mg/kg/day; LEL=0.5 mg/kg/day, (weight loss and convulsions); (Fitzhugh et al., 1964)

6) Teratology - mouse: Teratogenic NOEL=6.0 mg/kg/day (HDT, gestational days 7-16); Maternal LEL=6.0 mg/kg/day (HDT, decrease in maternal weight gain); Fetotoxic LEL=6.0 mg/kg/day (HDT, decreased numbers of caudal ossification centers and increases in supernumerary ribs); (Chernoff et al., 1975). This study was not considered since 41% of the test dams died at the highest dose tested.

CONFIDENCE IN THE RfD

Study: Low Data Base: Medium RfD: Medium

The principal study is an older study for which detailed data are not available

and in which a wide range of doses was tested. The chronic toxicity evaluati is relatively complete and supports the critical effect, if not the magnitude of effects. Reproductive studies are lacking. The RfD is given a medium confidence rating because of the support for the critical effect from other dieldrin studies, and from studies on organochlorine insecticides in general.

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1987. Dieldrin: Health Advisory. Office of Drinking Water, Washington, DC. NTIS PB 88-113543/AS.

Agency Work Group Review: 04/16/87

Verification Date: 04/16/87

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Walker, A.I.T., E. Thorpe and D.E. Stevenson. 1972. The toxicology of dieldrin (HEOD). I. Long-term oral toxicity studies in mice. Food Cosmet. Toxicol. 11: 415-432.

REVISION HISTORY

09/90 RfD Data: Text edited

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